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Editorial

Cardiogenic Shock in Acute Myocardial Infarction

THE RELIEF of shock is often the primary therapeutic objective and the critical determinant of survival in a patient with a severe attack of acute myocardial infarction. Yet the mechanism of shock in this disease is still obscure and its treatment unsatisfactory. The unsatisfactory treatment is due in large measure to uncertainty as to mechanism. Changing emphasis over the years on the therapeutic value of the Trendelenburg position, oxygen therapy, aminophylline, digitalis compounds, intravenous infusions of plasma or blood, intra-arterial transfusions, and vasopressor agents has reflected frequently altered concepts of the mechanism of the shock that accompanies acute myocardial infarction. Recent clinical and experimental observations have stimulated a review of these concepts to serve as a possible basis for rational therapy.

Differing reports of the incidence and mortality rate of shock in acute myocardial infarction attest both to the importance of shock as a major factor in death from myocardial infarction and to the lack of a generally acceptable definition or of uniform criteria that would permit consistent diagnosis. An analysis of 2,955 cases of acute myocardial infarction in 10 reported series revealed an over-all incidence of shock in 23 per cent with a fatality rate of 59 per cent in the cases with shock, representing approximately 13 per cent mortality among the total number of cases of acute myocardial infarction.[1] In six of the series in which presumably stricter criteria for shock were employed the incidence of shock varied from 7 to 20 per cent (average 14 per cent); death occurred in 79 per cent of the cases with shock, or 11 per cent of all the cases of myocardial infarction. In the other four series of cases of acute myocardial infarction presumably less strict criteria resulted in a reported incidence of shock in 52 per cent, which suggests the inclusion of less seriously ill patients; death occurred in 36 per cent of the cases of shock representing 19 per cent of the total number of cases. According to the varying criteria used, shock appeared to be responsible for or concerned in a fatality rate of either 11 per cent or 19 per cent of the cases of acute myocardial infarction.

An understanding of the mechanism of shock would be promoted by agreement as to the definition of shock and the acceptance of uniform criteria for its diagnosis. Unfortunately precise definition and criteria are hampered because shock represents a clinical syndrome subject to varied interpretation. Generally the diagnosis of shock is based on the recognition of its two essential elements: (1) a circulatory disturbance associated with a reduction in blood volume, venous return, or cardiac output by 30 to 40 per cent or more within a period of minutes to a few hours; i.e., rapidly but not suddenly; (2)

From the Division of Cardiology, Department of Medicine, The Mount Sinai Hospital, New York, New York.

resulting clinical manifestations caused by altered hemodynamics and changes in autonomic and other regulatory homeostatic mechanisms. The first heading includes the clinical settings that are likely to be associated with shock, such as severe hemorrhage, trauma, burns, diabetic acidosis, Addisonian crisis, and severe infection, as well as acute myocardial infarction. The second heading includes hypotension, cold, sweating skin, rapid thready pulse, weakness and mental torpor, and marked oliguria. The central objective finding is the hypotension but there is disagreement about the significant level. Maximal uniformity would be attained in the diagnosis of shock if a systolic blood pressure below 80 mm. Hg were required even if there are occasional exceptions. The preexisting level and the extent of fall in blood pressure may have some significance but these are too variable and should be disregarded. On the other hand the presence of a systolic blood pressure below 80 mm. Hg is significant of shock only in the presence of the clinical setting that can produce shock and the clinical manifestations listed above.

The term cardiogenic has been applied to the shock that accompanies acute myocardial infarction. Although this term has a justifiable basis, it should not lead to unwarranted inferences. Circulatory failure was once classified as cardiac and peripheral. Peripheral vascular failure was considered synonymous with shock. The term cardiogenic indicated that cardiac dysfunction could represent the primary disturbance responsible for shock, as distinguished from the noncardiac ("peripheral") vascular disturbances, such as hemorrhage, trauma, burns, infections, etc. The introduction of the term cardiogenic shock has occasionally led to two misinterpretations: (1) that there are two types of shock—cardiogenic and peripheral; (2) that cardiogenic shock unlike other forms of shock is accompanied by heart failure.

Undoubtedly the initiating mechanism in shock with myocardial infarction differs from that in other forms of shock, but the subsequent functional disturbances that actually produce the clinical picture of shock are essentially the same in all. The basic disturbance is a sharp diminution in cardiac output, which in myocardial infarction is due to a deficiency in myocardial contraction, in other cases such as hemorrhage to a sharp reduction in circulating blood volume, and in still others such as severe infection to a substantial diminution in venous return caused by venocapillary pooling. In all cases the clinical picture results from the deficient blood flow to various tissues caused by the reduction in output, to the fall in blood pressure to low levels and consequent inadequate perfusion of organs, and to sympathetic vasoconstriction and other reflex or humoral adjustments to these hemodynamic changes. Therefore the cardiogenic shock of myocardial infarction differs from the other types of shock only in the initiating cause, namely, acute myocardial infarction.

The concept that features of congestive heart failure are present in cardiogenic shock has been used as the basis for both diagnosis and treatment. The association of signs of pulmonary congestion and of a high venous pressure with those of shock is indicative of cardiogenic rather than of other forms of shock. Furthermore, the treatment of cardiogenic shock according to this concept would require measures similar to those for the treatment of congestive heart failure, especially digitalization.[2, 3] But in many cases of cardiogenic shock in myocardial infarction there are no overt symptoms and signs of pulmonary congestion and the venous pressure is normal, and although the manifestations of congestive heart failure may be ameliorated by digitalization, those of shock are not.

The role of sympathetic vasoconstriction in the shock syndrome was long regarded as of major importance. Aside from the hypotension that resulted from the fall in cardiac output the other clinical manifestations, including the cold, moist skin, especially of the extremities, were regarded as evidence of sympathetic stimulation. Sympathetic vasoconstriction was interpreted as a protective

mechanism that drew in the circulatory boundaries from the periphery and reallocated the diminished, available blood flow to the heart and brain by diverting it from the periphery, the skin, and the splanchnic organs. It was reported that the same degree of induced hemorrhage that resulted in shock in the normal dog was not followed by shock if the same animal was previously sympathectomized, even though the blood pressure was reduced to a lower level and for a longer period than in the normal dog.[4] It was concluded that sympathetic vasoconstriction was essential for the shock syndrome.

The purported essential role of sympathetic vasoconstriction in shock also influenced our concept of therapy. For a long time there appeared to be no rational indication for the use of sympathomimetic vasopressor agents, since it was believed that the presence of shock already indicated maximal vasoconstriction. When, more recently, favorable reports were made of the action of vasopressor drugs in the treatment of shock in myocardial infarction, this was explained by a direct action of these agents on the heart itself with improvement in cardiac contractility and stroke output.[5]

Recent changes in our concept of the mechanism and treatment of shock in acute myocardial infarction have been based on three types of observations: (1) measurements of hemodynamic functions in clinical and experimental myocardial infarction with shock,[6-12] (2) hemodynamic studies in experimental myocardial infarction with support of the circulation by an extracorporeal pump,[13] and (3) clinical observations on the effects of treatment.[1, 14]

Hemodynamic studies in patients with shock due to acute myocardial infarction have demonstrated no significant change in the circulating blood volume. Even when reductions were observed, the degree of reduction, approximately 15 per cent, is inadequate to result in shock. When congestive heart failure was associated with shock or developed later, the blood volume was increased. On the other hand the cardiac output has been regularly found to be sharply diminished, but in varying degree. The reported cardiac indices in patients with myocardial infarction in shock varied from 0.6 to 2.4 L./M.^{2} per minute, a diminution of approximately 25 to 80 per cent. Although shock appeared to occur regularly with the most severe reductions in cardiac output, moderately severe diminutions identical with those found in these patients with shock have been reported in other patients with myocardial infarction in whom shock did not develop. This suggested the importance of other factors besides a reduction in cardiac output. Since, according to the classical viewpoint, vasoconstriction is an essential feature of shock, a rise in peripheral vascular resistance is to be anticipated. The peripheral vascular resistance, as calculated from the cardiac output and mean arterial pressure, has been found normal in shock with myocardial infarction almost as often as it was elevated. As a rule, the peripheral vascular resistance was normal or only slightly increased in those cases of shock in which the diminution in the cardiac output was relatively less striking, suggesting that an inadequate increase in resistance as well as a fall in cardiac output determined the occurrence or absence of shock. A consideration of the relationships of mean arterial pressure (MAP), peripheral vascular resistance (R) and cardiac output (CO), namely $MAP = CO \times R$ discloses that the fall in blood pressure to the low level that characterizes shock can occur only if the reduction in cardiac output is not compensated by an adequate increase in R. With very severe reductions in CO, even substantial increases in R rarely suffice; with only moderately severe reductions in CO the blood pressure does not fall low enough and shock does not appear if the resistance remains normal or increases only moderately.

Similar conclusions were drawn from studies of experimental shock induced in closed-chest dogs by sending emboli of plastic microspheres into the coronary arteries.[12] Coronary shock, characterized by a fall in MAP of about 40 per cent, occurred in those

animals in which there was a similar fall in cardiac output but no significant change in resistance. In other animals in which a similar fall in cardiac output was not accompanied by a fall in blood pressure the resistance was found to be increased to the same degree that the cardiac output had fallen. These clinical and experimental observations of the hemodynamics of shock in acute myocardial infarction cast doubt on the concept of the essential nature of vasoconstriction for the development of shock and, on the contrary, attribute the development of shock to absence of or inadequate vasoconstriction, as measured by the systemic arterial resistance. Since there is clinical evidence of vasoconstriction in coronary shock, it is possible that this is relatively slight in its effect on peripheral vascular resistance or that vasoconstriction in some areas is neutralized by vasodilatation elsewhere. From the viewpoint of therapy these observations and considerations indicate that measures that increase the peripheral resistance in shock should be beneficial.

The importance of the peripheral resistance in determining the development or absence of shock in acute coronary occlusion was indicated more directly in recent observations on closed-chest dogs in which shock levels of hypotension were induced by coronary embolization.[13] The severe hypotension was associated with a corresponding fall in cardiac output without a rise in peripheral vascular resistance. Pumping large volumes of blood from the superior vena cava into the abdominal aorta did not produce a rise in central aortic pressure and coronary perfusion. A sustained rise in central aortic pressure was attained, however, when the peripheral resistance was increased by obstructing the abdominal aorta with a balloon catheter introduced via a femoral artery, the distal aorta below the site of obstruction being supplied by blood pumped from the superior vena cava. This rise in central aortic pressure was effected, despite a reduction in cardiac output to the upper aortic segment and only a slight increase in total blood flow, including that pumped to the aortic segment below the obstruction. These experimental observations not only add support to the importance of increasing the systemic arterial resistance in order to overcome the hypotension of shock but also indicate a possible direct therapeutic approach.

The effectiveness of sympathomimetic pressor drugs in elevating the low blood pressure in shock associated with acute myocardial infarction has provided clinical evidence that sympathetic vasoconstriction is inadequate in shock and can be increased by drug therapy, and supports the concept that shock occurs when the peripheral vascular resistance cannot be sufficiently increased to compensate for a rapid and severe fall in cardiac output. The former objection, that vasoconstrictor drugs could not be effective because intense vasoconstriction is already part of the shock syndrome, appears untenable in view of the frequent observation that a blood pressure that is too low to measure clinically can be promptly elevated to normal levels by the infusion of a sympathomimetic drug such as levarterenol, falls promptly when the infusion is discontinued, and rises again with a resumption of the infusion. Although a direct cardiac effect of increased stroke output may be contributory, there is no doubt that the major action of these drugs is to increase the peripheral vascular resistance by arteriolar vasoconstriction.

Although a substantial pressor effect can usually be obtained with vasoconstrictor drugs, relief of shock in myocardial infarction for a period of at least 12 hours after the drug is discontinued is accomplished much less frequently and the incidence of survival is even lower.[1] Thus the maintenance of a satisfactory blood pressure is not synonymous with the persistent relief of shock. It is probable that the maintenance of the blood pressure provides the needed perfusion of the cerebral and coronary arteries and tides the patient over the period of shock until the basic cause is overcome and a stable circulation is restored. It is uncertain why increasing doses of pressor agents sometimes are ineffective in producing or maintaining an adequate

blood pressure; it is possible that in such cases a satisfactory result may be obtained by extracorporeal support of the circulation with increased systemic arterial resistance provided by some method such as balloon obstruction of the lower abdominal aorta.

Correction of the severe hypotension that characterizes shock may be accomplished either by increasing the peripheral vascular resistance or by increasing the cardiac output. The sympathomimetic drugs, which appear to be frequently effective in all forms of shock, accomplish their pressor effect by increasing the peripheral vascular resistance. This action corrects a deficient compensatory mechanism (lack of increase of peripheral resistance) but does not significantly improve the severe reduction in cardiac output, which is the fundamental disturbance in shock. Measures that induce a substantial increase in cardiac output may be more likely to relieve shock rather than those that merely raise the arterial pressure by increasing resistance. To accomplish this, therapy must be directed toward the basic causes responsible for the fall in cardiac output, and unlike measures designed to increase peripheral resistance, varies with the different types of shock. Accordingly blood plasma or fluid and electrolytes are indicated when the fall in cardiac output is due to a deficient venous return caused by a loss of circulating blood volume; the causative infection must be overcome to relieve any associated shock; and mechanical hindrances must be alleviated when shock is caused by their impediment to cardiac filling or emptying. But there is at present no effective means of satisfactorily elevating the inadequate cardiac output caused by acute myocardial necrosis which is primarily responsible for the shock in these cases. The recommended use of digitalis has not been justified by the results, although digitalis may be effective for congestive heart failure, which may also be present. Similarly, the formerly employed intravenous or intra-arterial transfusions have had no more than transient effects, presumably because there is no consistent or significant deficiency in circulating blood volume and these measures do not correct the myocardial factor responsible for the deficient cardiac output. In such cases of cardiogenic shock that are unresponsive to other measures, mechanical obstruction to the lower aorta to provide the necessary increase in systemic arterial resistance and support of the circulation by an extracorporeal pump until cardiac function stabilizes, may become a necessary and effective practical measure. Such procedures are experimental at the present time and are chiefly of interest because of their contribution to the understanding of the pathogenesis of shock in myocardial infarction and not because of any proved clinical benefit.

CHARLES K. FRIEDBERG

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Aneurism of the Aorta; Singular Pulsation of the Arteries, Necessity of the Employment of the Stethoscope

By Dominic John Corrigan, M.D.

Lecturer on the Institutes and Practice of Medicine; one of the Physicians of the Sick-Poor Institution, Dublin.

A trite objection frequently made to the stethoscope, and which those who put it would consider peculiarly applicable to this case, is the second.

Granting that the practical organic lesion were discovered by the stethoscope, the disease is inevitably fatal; what, then, is the use of the discovery? This is an objection that should never come from the lips of a man of science. In the pursuit of science every truth, every fact discovered, is of value. We may not, in every case, see its immediate application, or instant practical good result, but it is a step gained. We know not how soon it may become important, or whether, although yet unknown to us, it may but be the way to a hitherto unexplored field of knowledge. It is only for those of narrow minds to say, that facts, or means of attaining facts, should be disregarded, because there is not some immediate obvious practical result.—*The Lancet* 1:586, 1829.

Atrial Infarction of the Heart

By CHI KONG LIU, M.D., GILBERT GREENSPAN, M.D., AND RONALD T. PICCIRILLO, M.D.

CLINICAL REPORTS of atrial infarction diagnosed during life are few. This may be due to two major factors. First, the clinical features of isolated atrial infarction are not known, for it is usually associated with ventricular infarction, which dominates the clinical picture. Secondly, the diagnosis of atrial infarction can be made only from the electrocardiogram by small, transient elevations[1] and reciprocal depressions of the P-Ta segment usually associated with changes in configuration of the P wave.

Langendorf,[2] in 1937, reported one case of atrial infarction found at autopsy that in retrospect could have been recognized ante mortem from electrocardiographic changes. Subsequently, the electrocardiographic manifestations of atrial infarction in the standard leads were described[3-6] in cases in which necropsy evidence had prompted a retrospective reinterpretation of the electrocardiogram.

Hellerstein,[7] in 1948, reported the first case with the correct ante mortem diagnosis of atrial infarction confirmed by necropsy, and other cases were subsequently reported.[8-10] The number of cases described, however, is far below the anticipated percentage of 3 to 17 reported by others.[3, 11, 12]

The purpose of this paper is to present the changes in the 12-lead electrocardiogram from six cases of atrial infarction associated with ventricular infarction, which were diagnosed clinically and confirmed by autopsy.

Case Reports

Case 1

A 54-year-old diabetic, hypertensive woman entered the hospital because of mental confusion and convulsive seizures. Four days later rapid atrial fibrillation developed that stopped shortly after intravenous lanatoside C. The P waves were of the negative-positive type in lead I, predominately negative in V_1, and largely positive in V_3 (fig. 1a). Changing contour of the P wave in lead I suggested a wandering pacemaker. The P-Ta segment was depressed in leads III, aV_F, V_1, and V_2, and was elevated in leads I, aV_L, V_5, and V_6. Complete left bundle-branch block was present. A diagnosis of atrial infarction was made. The characteristic P-Ta changes in aV_L and V_5 almost completely disappeared during the next 3 days (fig. 1b). The patient died 3 weeks later in coma. The serum glutamic oxaloacetic transaminase levels were 62 and 36 units.

Necropsy revealed a 1-cm.^{2} hemorrhagic area on the endocardial surface of the anterolateral wall of the right atrium, at the atrioventricular junction. Small hemorrhagic areas, 2 mm. in diameter, were seen on the endocardial surface of the left atrium. The left circumflex coronary artery near its origin was completely occluded.

In the atrial myocardium (fig. 2) were several areas of hemorrhagic necrosis surrounded by a mild neutrophilic and lymphocytic infiltration. There was moderate patchy fibrosis. The left ventricular myocardium showed necrosis.

Case 2

A 54-year-old white man entered the hospital complaining of chest pain with shortness of breath for 2 weeks. The electrocardiogram revealed incomplete left bundle-branch block (fig. 3), occasional premature atrial contractions, and a brief run of atrial tachycardia at 160 per minute. The P-Ta segment was depressed in leads II, III, aV_F, all the precordial leads, and elevated in aV_L. The P waves were of the positive-negative variety in V_1. The serum glutamic oxaloacetic transaminase levels were 58 and 56 units. Since there was no evidence of acute ventricular myocardial infarction, a diagnosis of isolated atrial infarction was made. The patient was digitalized for mild congestive heart failure. He died suddenly 2 days later.

Autopsy revealed severe generalized coronary arteriosclerosis with a recent thrombus occluding the left anterior descending coronary artery and an old occluding thrombus of the right coronary artery. An extensive infarction was seen in the ventricular septum from the anterior to the posterior wall of the left ventricle. The hemorrhagic area of the left ventricle extended into the left

From the Departments of Medicine, Los Angeles County Harbor General Hospital, Torrance, California, and the University of California at Los Angeles, California.

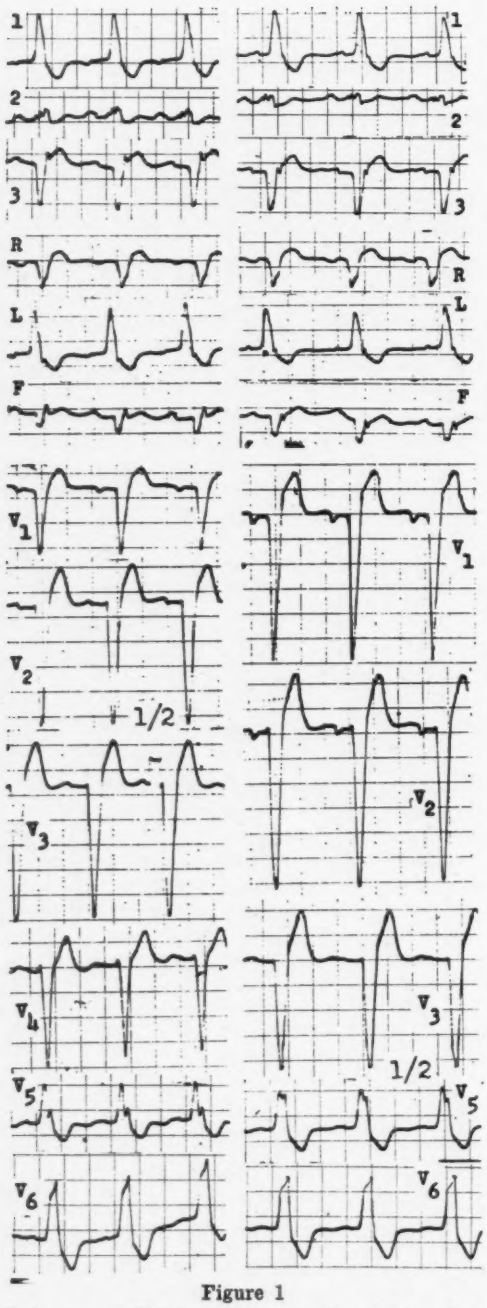

Figure 1

Left, case 1. Electrocardiogram 30 minutes after lanatoside C shows abnormal P and P-Ta waves and complete left bundle-branch block. Right, Case 1. Notched P waves are seen in lead I. P-Ta segments in aV_L and V_5 have almost returned to normal.

posterior atrial wall and appendage. Grossly the right atrium appeared normal.

Microscopically both atria showed perivascular lymphocytic infiltration, hemorrhage, necrosis, and hyalinization of the muscle fibers, typical of infarction (fig. 4).

Case 3

A 62-year-old white woman with severe ulcerative colitis, developed tachycardia with occasional premature beats, dyspnea, chest pain, and congestive heart failure. The next day the patient had more cardiac pain, transient multifocal atrial tachycardia of 200 per minute and hypotension. An electrocardiogram (fig. 5) at that time revealed a septal and inferior ventricular myocardial infarction. The P waves in lead II were wide and slurred and 1.25 mm. high in lead II. In V_1 and V_2 the P waves were diphasic and were followed by a depression of the P-Ta segment of 1.5 to 1.8 mm. The P waves were notched in V_3 and V_4 and low and notched in V_5 where the P-Ta segment was elevated 1.0 to 1.5 mm. The P wave in V_6 was wider and the P-Ta segment was slightly elevated. The deviations of the P-Ta segments in V_5 and V_1 and V_2 probably represented reciprocal changes of an atrial injury current. A definite diagnosis of left atrial infarction was made. The patient died 4 hours later in shock.

Necropsy showed a 1 by 2 cm. area of hemorrhage in the left atrium and infarction of the interventricular septum. The coronary arteries showed only slight arteriosclerosis, with no occlusion. Microscopically congestion of the vessels and hemorrhages into interstitial tissue were compatible with an early stage of atrial infarction.

Case 4

A 52-year-old white man had repeated episodes of congestive heart failure for 4 years. An electrocardiogram (fig. 6) revealed incomplete left bundle-branch block and evidence of left ventricular enlargement. The P-R interval was 0.22 second. The P waves were notched in I, II, III, and aV_F with depression of the P-Ta segment. In aV_L the P-Ta segment was elevated 0.5 mm. The P waves in V_1 and V_2 exhibited a slight positive and wide negative wave with a total duration of 0.11 second. A diagnosis of atrial infarction was suggested.

Three weeks later chest pain and increased failure occurred. The serum glutamic oxaloacetic transaminase levels were 207 and 316 units, and the white blood count and temperature were elevated. An electrocardiogram showed changes in the P waves and P-Ta segments. The P waves in leads V_{1-3} were biphasic and 0.10 second wide; in leads I, II, and aV_F, the terminal portions of the P waves were depressed and notched. The P-Ta segments were depressed in leads I, II, III, aV_F, and V_6 and elevated in aV_R. Terminally the P-Ta seg-

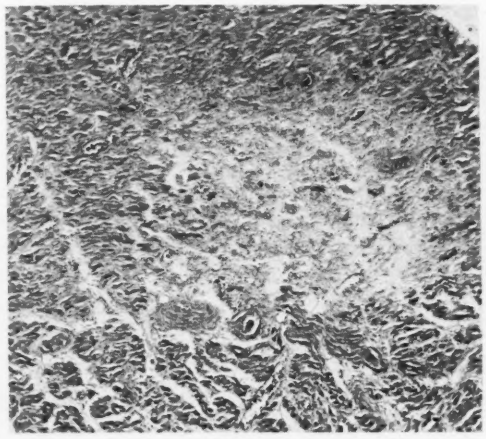

Figure 2

Case 1. Section of the atrium shows focal fibrosis and necrosis of the myocardium with polymorphonuclear infiltration.

ment became more depressed in lead I, and the terminal part of the P wave was more negative, being depressed 4 mm. in V_1.

At autopsy the heart weighed 650 Gm. A 2 by 2 cm. clot was adherent to the posterior surface of the right atrium. Thrombi were also present on the posterior wall of the left ventricle. The coronary arteries showed extensive arteriosclerotic changes. Moderate interstitial fibrosis was present histologically. An area of acute inflammatory change with necrosis was seen under the mural atrial thrombus.

Case 5

A 79-year-old white man was admitted to the hospital because of chest pain of 2 weeks' duration associated with nausea and vomiting. He had basilar rales but no other signs of congestive heart failure. Leukocytosis was present initially, and the sedimentation rate became elevated. An initial electrocardiogram (fig. 7) showed subendocardial injury of the posterior surface of the left ventricle. The P-Ta segments were depressed 1 mm. in leads V_{1-3} and elevated from 1.0 to 1.5 mm. in leads V_5 and V_6. The P-Ta segments in the limb leads were obscured by a changing T-P baseline. These changes in the P-Ta segments varied in subsequent tracings and a diagnosis of atrial infarction was made. The patient became cyanotic and hypotensive and died in 1 week. The serum glutamic oxaloacetic transaminase levels varied from 17 to 34 units.

At autopsy the heart weighed 300 Gm. The myocardium of the left and right ventricle was flabby and contained numerous petechiae and focal hemorrhages as did the posterior third of the interventricular septum. There were also hemorrhages in the posterior wall of both atria extending down to the atrioventricular junction. The right coronary artery was occluded 3 cm. from its origin by a thrombus and the left circumflex was occluded by a fresh thrombus. Histologic sections showed changes of acute myocardial infarction with necrosis and a large area of subepicardial atrial hemorrhage.

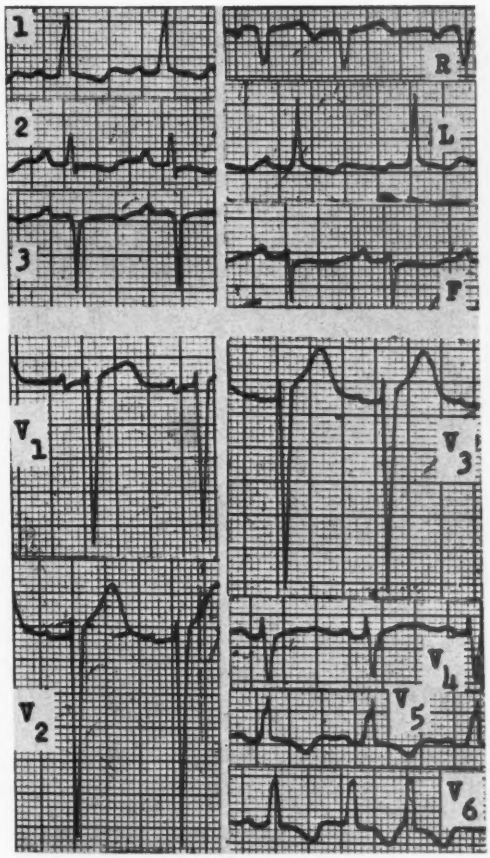

Figure 3

Case 2. Electrocardiogram shows incomplete left bundle-branch block and no evidence of acute ventricular infarction and P-Ta segment deviations. An atrial premature beat is seen in V_6.

Case 6

A 72-year-old white man entered the hospital because of severe congestive failure and pain in the arms of 1 week's duration. Moderate congestive heart failure followed a myocardial infarction 3 years earlier. A leukocytosis of 23,000 per mm.^{3} and a serum glutamic oxaloacetic transaminase level of 26 units were present on admission. An electrocardiogram (fig. 8) revealed sinus tachy-

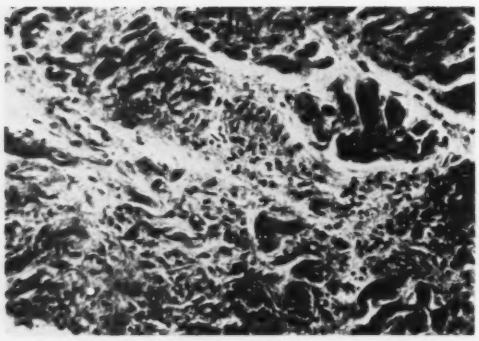

Figure 4

Case 2. Section of the atrium shows congestion of the small vessels with hemorrhage and necrosis and hyalinization of the muscle fibers.

cardia with a wandering pacemaker, premature atrial beats, and rare premature ventricular beats. The P wave was positive-negative in V_{1-3}. There was also evidence of apical myocardial infarction, age undetermined. Subsequently supraventricular tachycardia and electral alternans appeared (fig. 8, lower). A diagnosis of atrial infarction was made. Finally ventricular tachycardia appeared and the patient died.

At autopsy the heart weighed 750 Gm.; it showed bilateral hypertrophy, an old scar at the apex, and a mural thrombus in the right atrium. The proximal portion of the left coronary artery was slightly narrowed by a calcium plaque. Histologic sections revealed the old apical infarction of the ventricle and showed an atrial infarction under the mural thrombus with subendocardial necrosis.

Results and Discussion

The clinical diagnosis of atrial infarction was made correctly ante mortem in six cases from the electrocardiogram. Both atria were involved in cases 1, 2, and 5, the right atrium alone in cases 4 and 6, and the left atrium in case 3. All cases had associated ventricular infarction. Changes of the P-Ta segment in the precordial leads were especially helpful in cases 1, 3, and 5. The diagnosis of atrial infarction is easily missed because the changes are less dramatic than those of the ventricular infarction usually accompanying it. Consequently relatively few cases have been reported in the literature, despite the reported incidence of 1 to 17 per cent among ventricular myocardial infarctions.[3, 13, 14] The wide range may be due to the varying care and criteria for its autopsy diagnosis. The atrium underlying a mural thrombus is probably rarely sectioned for histologic study, and in cases of ventricular infarction with grossly normal atria, histologic sections of the atria are seldom made.

Atrial infarctions produced experimentally in dogs and cats have been studied by Abramson[15] and several other investigators,[16-19] but the diagnostic electrocardiographic criteria have not been agreed upon. Elevations and depressions of the P-Ta segment have been of prime importance in the diagnosis of this condition. Analysis of the electrocardiograms of the patients presented shows that the P-Ta segment, when plotted vectorially, is directed toward the area of atrial infarction. This may be analogous to the direction of the current of injury (S-T segment) in ventricular infarction.[20] Therefore this segment might be called P-STa-Ta rather than the P-Ta segment. Because there is little atrial gradient,[21] a direct comparison between ventricular repolarization and atrial repolarization may not be possible. For want of a better term, we use the P-Ta segment with the above understanding. The P-Ta segment usually extends through the QRS and S-T sections of the electrocardiogram, so that its complete examination is impossible unless complete heart block is present.

In our only case of isolated right atrial infarction (case 4, fig. 6) the P-Ta segment vector was directed to the right atrium and posteriorly. The P-Ta segment was depressed in leads I, II, III, aV_F, V_1, V_2, and occasionally V_3. It became isoelectric in lead V_6. It was elevated in leads aV_R and aV_L. In isolated left atrial infarction (case 3, fig. 5) the P-Ta segment was depressed in leads II, III, aV_F, V_1, V_2, and elevated in I, aV_R, aV_L, V_5, and V_6. In bilateral infarction the direction of the P-Ta segment vector may depend on which atrium is infarcted the more. In cases 1 (fig. 1) and 5 (fig. 7) (bilateral atrial infarction) the P-Ta segment vectors pointed to the left atrium and thus cannot be distinguished from isolated left atrial infarction.

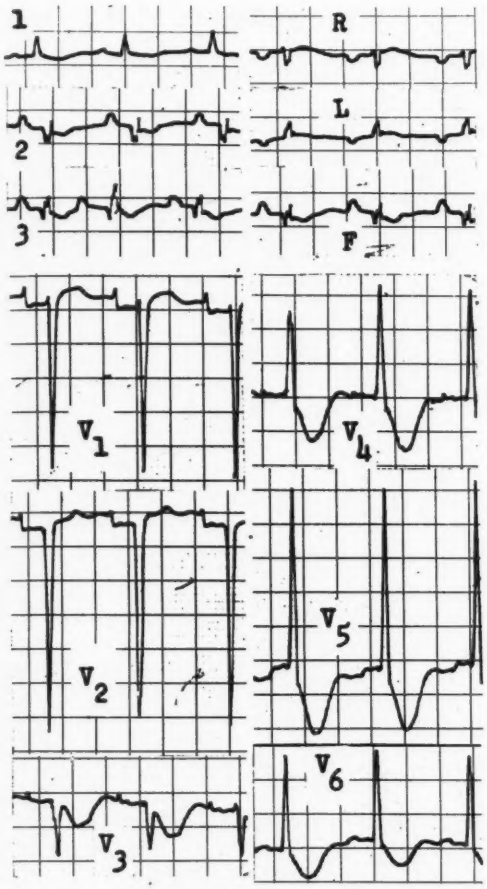

Figure 5

Case 3. Electrocardiogram shows P and P-Ta deviations and anteroseptal and diaphragmatic myocardial infarction.

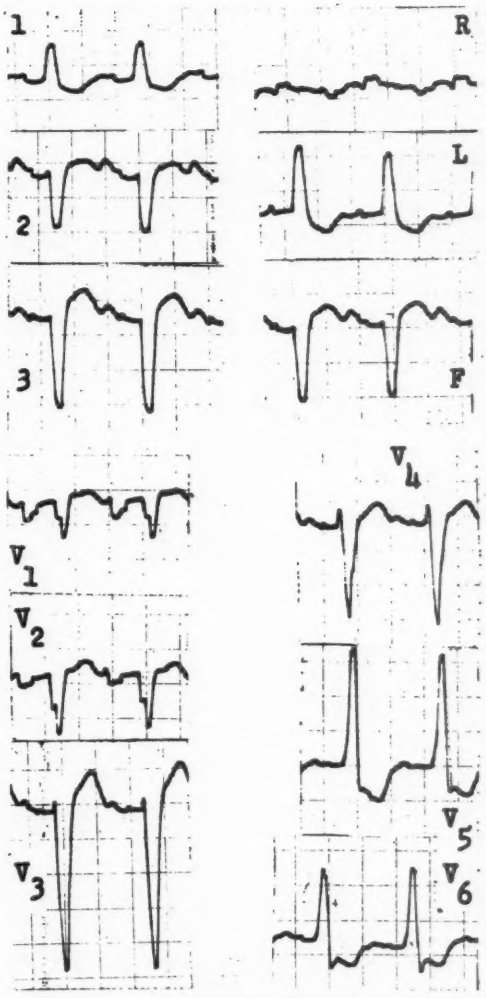

Figure 6

Case 4. Electrocardiogram shows depressed segments in leads I, II, III, and aV_F, positive-negative P waves in V_1, and V_2, notched P wave in V_2 and V_4, and some intraventricular block.

In case 6 (fig. 7) there was no definite P-Ta segment vector that could be plotted. In this case, only supraventricular arrhythmias were present, which with the clinical picture of ventricular myocardial infarction led to the ante mortem diagnosis of atrial infarction as well. In this case the right atrium alone was involved where the sinoatrial node is located. It would be of interest to collect enough cases of left and right atrial infarction to determine whether these arrhythmias were more common in right atrial infarction.

Atrial arrhythmias are very common in our cases of atrial infarction as well as those reported in the literature. The importance of a small infarction of the right atrium near the sinoatrial node has been stressed by Young and Koenig[6] and could account for death by arrhythmia, despite its small size.

The beginning of the P waves may be fused with the T and U waves, especially in sinus tachycardia. The Q of the P has

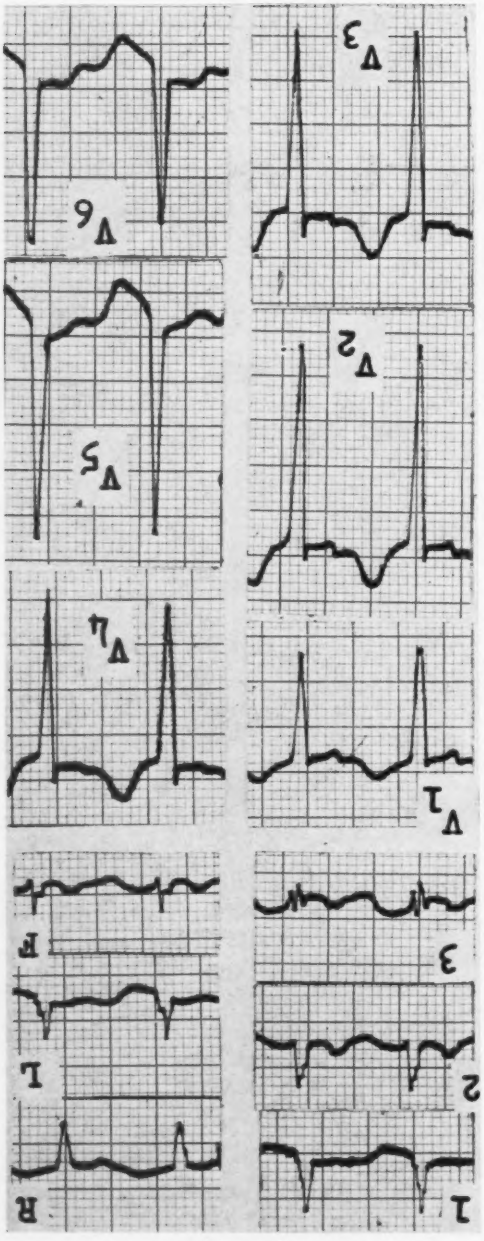

Figure 7

Case 5. There is a depression of the P-Ta segment in V_1 to V_3, and elevation in V_5 and V_6.

been described[18] as in ventricular infarction, its vector may point away from the infarcted area. In case 3 in V_4 a negativity before the P might represent the atrial Q wave. It is at times difficult to determine where the P wave ends and the P-Ta segment begins, particularly in the right precordial chest leads and in tachycardia with short P-R interval. Often the end of the P wave merges with the P-Ta segment so that a clear separation is not possible. Some cases of atrial infarction reported in the literature[4, 5, 9]

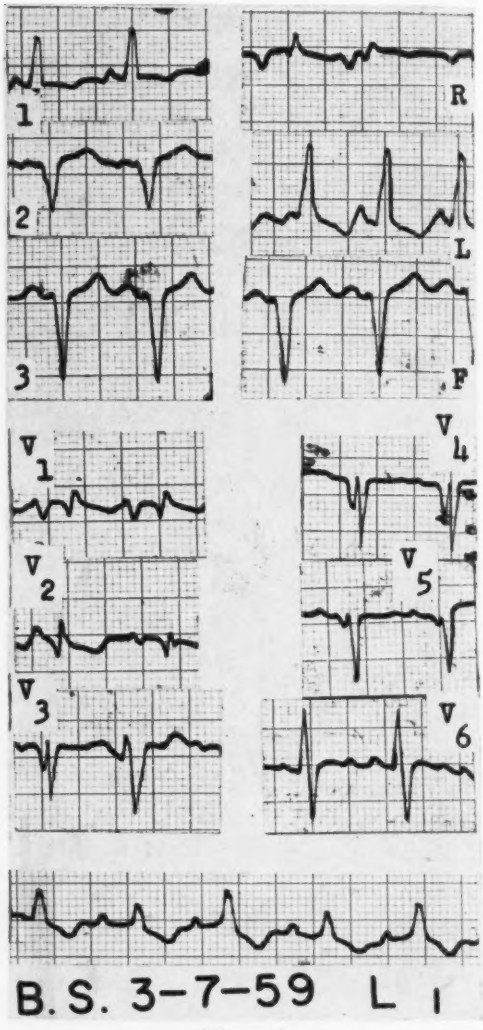

Figure 8

Case 6. Sinus tachycardia with wandering pacemaker and electrical alternans in a subsequent (lower) strip. Also present is an old apical myocardial infarction.

present P-Ta segment elevations in leads II, III, and aV_F. These cases probably correspond to more inferior-posterior locations of the atrial infarction. Notching, widening, peaking, slurring, and positive-negative or negative-positive biphasic P waves are more difficult to evaluate in localization of atrial infarction.

The changes in the P-Ta segment in atrial infarction may last for only a few hours or a few days. In case 1, elevation of the P-Ta segment almost returned to the isoelectric line in 1 day. Complete electrocardiograms are advisable while the patients are having atrial premature beats, wandering pacemaker, or other forms of atrial arrhythmias. If atrial infarction is suspected, an electrocardiogram should also be taken immediately after sinus rhythm has resumed following supraventricular tachycardia or paroxysmal atrial fibrillation.

In our series, the left atrium was involved by infarction in all cases except cases 4 and 6. This is not in agreement with the reported incidence of the literature of more right-sided than left-sided lesions. Theoretically, one would expect to have a greater incidence of left atrial infarction because of the greater incidence of left ventricular infarction.

All six cases had sinus tachycardia during their illness. Atrial arrhythmias occurred in all but case 5. Among the atrial arrhythmias cases 2, 3, and 6 had atrial premature beats and runs of atrial tachycardia, case 1 had supraventricular tachycardia and paroxysmal atrial fibrillation, and cases 1, 3, 4, and 6 had a wandering pacemaker. Atrial flutter was not observed in our series. We consider that any form of atrial arrhythmia occurring in patients with ventricular myocardial infarction is highly suggestive of an accompanying atrial infarction as in case 3.

The diagnosis of atrial infarction is not only of academic interest but also of some clinical importance. In case 2, a diagnosis of acute ventricular myocardial infarction could not be made from the electrocardiographic changes but atrial infarction could.

We strongly believe that all patients with electrocardiographic evidence of atrial myocardial infarction should be treated as if they had ventricular myocardial infarction because there may be ventricular involvement that does not show in the electrocardiogram.

The serum glutamic oxaloacetic transaminase levels were not helpful in the evaluation of isolated atrial infarction; in our cases elevations were always associated with ventricular infarction.

Since mural thrombi are so common in atrial infarction (2 of 6 cases) anticoagulant therapy seems indicated to decrease the probability of the formation of a mural atrial thrombus. Migration of atrial thrombi may be the cause of fatal cerebral or massive pulmonary infarction.

Summary

Six cases of atrial infarction associated with ventricular infarction are presented. All cases were diagnosed during life and were confirmed by autopsy.

A clinical diagnosis of atrial infarction should be suspected in patients with ventricular myocardial infarction having any form of atrial arrhythmia. Frequent electrocardiograms should be obtained, especially if sinus rhythm has just been re-established after episodes of supraventricular tachycardia or atrial fibrillation.

The *major* electrocardiographic criteria for the diagnosis of atrial infarction are as follows: elevation of the P-Ta segment of over 0.5 mm. in V_5 and V_6 with reciprocal depression of the same segment in V_1 and V_2; elevation of the P-Ta segment of over 0.5 mm. in lead I and its depression in leads II or III; depression of the P-Ta segment of more than 1.5 mm. in precordial leads and 1.2 mm. in leads I, II, and III in the presence of any form of atrial arrhythmia.

The *minor* electrocardiographic criteria in making the diagnosis of atrial infarction are as follows: abnormal P waves: M-shaped, W-shaped, irregular or notched; depression of the P-Ta segment of small amplitude without elevation of this segment in other leads cannot be regarded by itself as positive evidence of atrial infarction.

A diagnosis of atrial infarction can some-

times be made when the presence of ventricular myocardial infarction cannot be definitely established by electrocardiogram.

The treatment of atrial infarction is similar to that of ventricular infarction. Attention should be directed to the control of atrial arrhythmias and to the prevention of mural thrombi.

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Congenital Mitral Insufficiency

By Norman S. Talner, M.D., Aaron M. Stern, M.D., and Herbert E. Sloan, Jr., M.D.

THE INFREQUENT REPORTS of mitral insufficiency on a congenital basis reflect the apparent rarity of this condition. Aneurysmal dilatation of the left atrium in a 5-year-old girl with clinical findings suggesting mitral insufficiency has been described by Semans and Taussig in 1938.[1] Postmortem examination of this patient revealed thickening of the mitral and tricuspid valves, saccular dilatation of the left atrium, and cardiac hypertrophy. The chordae tendineae also were noted to be greatly shortened. Prior[2] has described two adults with congenital malformations of the mitral valve. In one, duplication of the mitral orifice was present while in the other the posterior leaflet lacked the proper chordal attachment. Kjellberg and co-workers[3] described the clinical and hemodynamic findings in three patients with congenital mitral incompetence. In two of these patients the left atrium was aneurysmally dilated and the appendage was prominent. In the third patient the malformation was present in association with corrected transposition of the great vessels. One of these patients died, and at postmortem examination the anterior cusp of the mitral valve was found to be lacking and the posterior cusp was rigid. Helmholz et al.[4] have described mitral insufficiency in association with corrected transposition of the great vessels. This has also been discussed by Anderson and associates[5] in their review of corrected transposition. Linde and Adams[6] reported mitral insufficiency in association with a patent ductus arteriosus in three patients, which they considered related to the presence of endocardial sclerosis involving the valve leaflets. Three patients with congenital mitral incompetence who underwent surgical repair were reported by Starkey.[7] In these patients dilatation of the mitral valve ring was the dominant feature. Surgical repair with the open-heart approach was advised as the procedure of choice. Edwards and Burchell[8] have described and classified the pathologic anatomy in congenital mitral insufficiency. This included inadequate valve substance as in isolated cleft of the anterior mitral leaflet and anomalous chordal insertion. The latter has been observed in association with the posterior leaflet, corrected transposition of the great vessels, endocardial sclerosis, and duplication of the mitral orifice.

Although rare, this abnormality may produce severe impairment of cardiac function necessitating surgical intervention. Ten patients with congenital mitral insufficiency have been evaluated at the University of Michigan Medical Center. This communication constitutes an analysis of the salient clinical, hemodynamic, and surgical findings in this group.

Clinical Material and Methods of Study

Ten patients have been studied. All had the typical clinical findings of mitral insufficiency. In six patients the diagnosis was confirmed at surgery (table 1). The mitral valve was explored and was found to be incompetent in one patient at the time of correction of a coarctation of the aorta. A left-sided catheterization in this patient had shown the characteristic left atrial pressure contour of mitral insufficiency. In two patients the diagnosis was confirmed at postmortem examination: one died while awaiting surgical repair; the other, with mitral insufficiency associated with corrected transposition and a ventricular septal defect, died during cardiotomy. The diagnosis was proved by left ventricular angiography in a last patient who is to have surgical correction.

Right heart catheterizations were carried out in

From the Departments of Pediatrics and Communicable Diseases and Surgery, University of Michigan Medical Center, Ann Arbor, Michigan.

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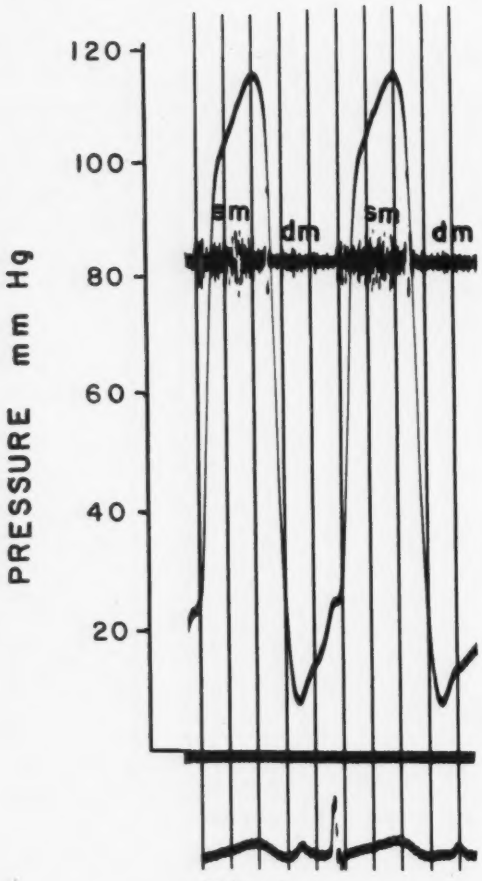

Figure 1

Case 5. Phonocardiogram showing typical apical pan-systolic and protodiastolic murmurs. The left ventricular end-diastolic pressure is elevated.

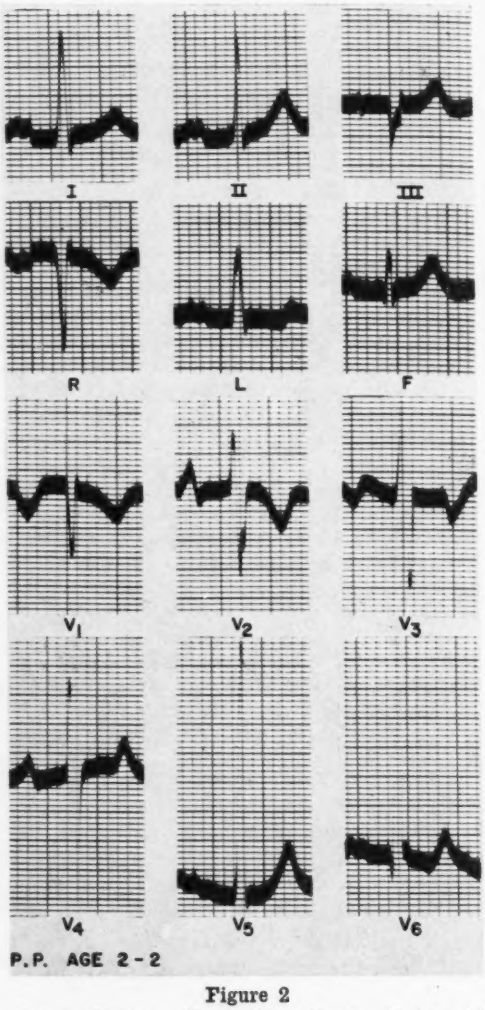

Figure 2

Case 2. Electrocardiographic evidence of left atrial (P mitrale) and left ventricular enlargement.

eight patients. Left heart catheterizations via the percutaneous method of Bjork and associates[9] were performed in three patients. In two patients a retrograde left heart catheterization as described by Vlad and Lambert[10] was done with injection of contrast media into the left ventricle.

Mitral incompetence was considered to be the major defect in all of the 10 patients. Three patients had an associated coarctation of the aorta, in two patients corrected transposition of the great vessels was demonstrated, and two patients also had evidence of a patent ductus arteriosus. We have not included patients with mitral incompetence in association with a patent ductus arteriosus in whom the latter defect was the primary abnormality.

Clinical Features

Nine of the 10 patients had at least one bout of congestive heart failure (table 1). Fatigue on exertion, retardation of growth, and frequent respiratory tract infections were present in all of the patients. In no patient could a history of manifestations of rheumatic fever be elicited. Eight of the 10 patients were examined by physicians during the first year of life and found to have a significant cardiac murmur. Two patients were not ex-

amined until age 5, when the murmurs were first detected. These patients had no evidence of rheumatic fever, were afebrile, had a normal erythrocyte sedimentation rate, and no elevation of the antistreptolysin titer.

The physical findings were also remarkably uniform. All had some degree of cardiomegaly. A prominent lateral apical out-thrust indicating left ventricular enlargement was usually seen. The typical pansystolic regurgitant murmur of mitral insufficiency was heard in every instance. Seven of the 10 patients had an associated apical thrill. An apical protodiastolic rumble was also heard in every patient. This murmur has been described in patients with mitral insufficiency and probably results from an increased flow across the mitral valve.[11] The typical murmurs are shown in figure 1. The pulmonary component of the second heart sound was thought to be accentuated in three instances, and this finding correlated with the level of the pulmonary artery pressure.

Electrocardiographic Findings

Table 2 summarizes the electrocardiographic findings. Evidence of left ventricular hypertrophy was present in six cases. Right ventricular hypertrophy was encountered in one patient who had corrected transposition of the great vessels and pulmonary hypertension. Another patient with corrected transposition had incomplete right bundle-branch block. Left atrial enlargement as indicated by the presence of a bifid P wave (P mitrale) (fig. 2) was encountered in all of the patients including the two with corrected transposition.

Roentgenologic Examination

The roentgen findings in this group of patients consisted primarily of left atrial and left ventricular enlargement. A double atrial contour, elevation and spreading of the mainstem bronchi, prominence of the left atrial appendage, and a posterior impression on the barium-filled esophagus were found as evidence of left atrial enlargement (fig. 3). In three instances the left atrium was aneurysmal in size. Left ventricular enlargement was suggested by protrusion of the apex beyond

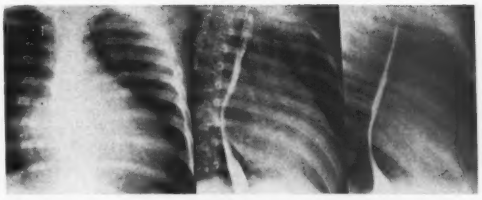

Figure 3

Case 7. Left. Considerable increase in over-all cardiac size, particularly of the left ventricle. Suggestion of a double atrial contour. Prominence of the central pulmonary vessels. Center and right. Marked enlargement of the left atrium.

the vertebral margins in the left anterior oblique projection. The aorta was characteristically small while the pulmonary vascular markings were either normal or slightly increased. The peripheral pulmonary vessels did not appear narrow in any of the patients, including those with significant pulmonary hypertension. No intracardiac calcifications were noted. In the two patients with corrected transposition, the upper left border of the hear (ascending aorta) presented as a gentle convexity having a more gradual slope than is usually associated with the pulmonary artery of a normal heart. This latter finding has been described by Anderson and associates[5] as a characteristic roentgenologic feature of corrected transposition.

Angiocardiography

All of the patients in the series had biplane angiocardiograms after injection of contrast material into a peripheral vein, pulmonary artery, or left ventricle. With the exception of the left ventricular injections, the studies were not diagnostic of mitral insufficiency, but they served to determine chamber size and the presence of associated defects. The left atrial chamber was usually markedly enlarged and formed the right cardiac border (fig. 4, upper). In addition, the right branch of the pulmonary artery was elevated by the enlarged left atrium (fig. 4, lower). We have also been impressed by the large volume changes encountered in the left atrium as demonstrated in systolic and diastolic exposures (fig. 5). Retrograde left heart

Table 1

Clinical Data

Case	Age (yr.)	Sex	Diagnosis established	Associated defects	Rheumatic fever	Ease of fatigue	Growth retardation	Congestive failure	Age murmur heard	Frequent respiratory infection
1. LA	7	F	surgery	0	0	+	+	+	5 yr.*	+
2. PP	4	M	surgery	patent ductus arteriosus	0	+	+	+	3 mo.	+
3. CP	8	F	surgery	0	0	+	+	0	5 yr.*	+
4. DP	6	M	surgery	corrected transposition	0	+	+	+	2 mo.	+
5. RJ	3	M	surgery	0	0	+	+	+	1 yr.	+
6. MB	5	M	surgery	coaretation	0	+	+	+	1 mo.	+
7. SE	9 mo.	M	post mortem	corrected transposition	0	+	+	+	8 mo.	+
8. MP	7	F	post mortem	0	0	+	+	+	2 mo.	+
9. DW	8	M	surgery	coaretation	0	+	+	+	1 mo.	+
10. SB	2	F	retrograde LV angiogram	patent ductus arteriosus	0	+	+	+	1.5 mo.	+

*First physical examination was pre-school physical

Table 2

Electrocardiographic Findings

Case	Rate	P-R interval	Axis	Right ventricular hypertrophy	Left ventricular hypertrophy	P mitrale
1. LA	120	0.15	+ 67	−	+	+
2. PP	110	0.20	+ 6	−	+	+
3. CP	88	0.14	+ 70	− Inc. RBBB	−	+
4. DP	100	0.18	+110	+	−	+
5. RJ	88	0.14	+ 8	−	+	+
6. MB	87	0.24	+113	−	+	+
7. SE	148	0.13	+ 65	+	−	+
8. MP	133	0.15	+ 81	−	−	+
9. DW	92	0.14	+100	−	+	+
10. SB	126	0.14	+ 84	−	+	+

catheterization with injection of contrast material* into the left ventricle demonstrated regurgitation of contrast material into the left atrium in two instances. This is the technic we presently prefer for proving mitral regurgitation (figs. 6 and 7). These studies were carried out with electrocardiographic monitoring so as to correlate the angiocardiographic findings with phases of the cardiac cycle and to rule out the possibility that regurgitation could have occurred because of premature ventricular contraction during atrial systole.

*The contrast material used was the Ditriokon brand of sodium diprotrizoate and diatriazoate injection, supplied by Mallinckrodt Chemical Works.

Right Heart Catheterization

The findings obtained at right heart catheterization are shown in table 3. In only one patient was the pulmonary artery pressure within normal limits. One patient had severe pulmonary hypertension, whereas in the others moderate elevation of the pulmonary artery pressure was encountered. The pulmonary capillary wedge pressure was elevated in five of the patients studied in whom this pressure could be obtained. In three instances

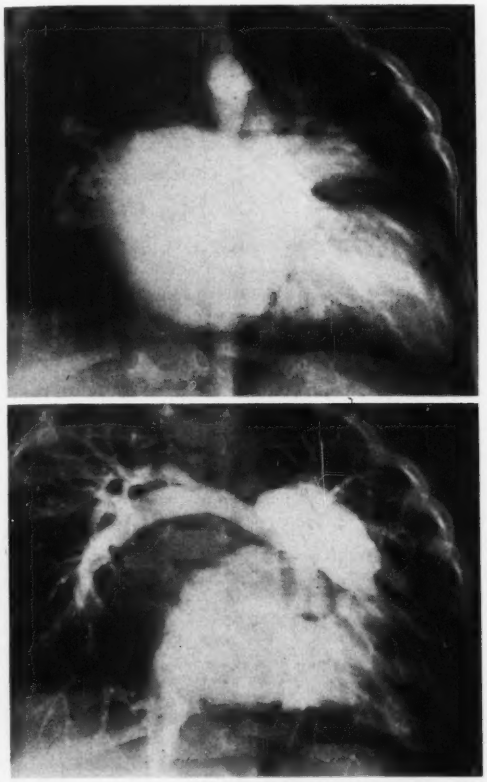

Figure 4

Case 2. Upper. Marked increase in the size of the left atrium, which forms the right cardiac border. Lower. Elevation of the right branch of the pulmonary artery by the enlarged left atrium.

the diagnosis of mitral incompetence could be suspected on the basis of the wedge pressure pulse contour. In these patients there was elevation of the V wave and a rapid y descent. The remainder of the patients showed nonphasic tracings not suitable for contour analysis.

Left Heart Catheterization

The data obtained at left heart catheterization are summarized in table 4. The left atrial pressure pulse contour was analyzed by two methods utilized in acquired mitral disease to differentiate mitral stenosis from mitral insufficiency. These are the ratio of the pressure at the peak of the V wave to that at the peak of the A wave, and the ratio of the y descent in the first 0.1 second to the mean left atrial pressure.[12] In each of the patients the ratio of the V to A wave was greater than 1.4 and the ratio of the y descent in the first 0.1 second to the mean left atrial pressure equaled or exceeded 0.5, supporting the diagnosis of mitral insufficiency. A typical left atrial pressure pulse contour is seen in figure 8.

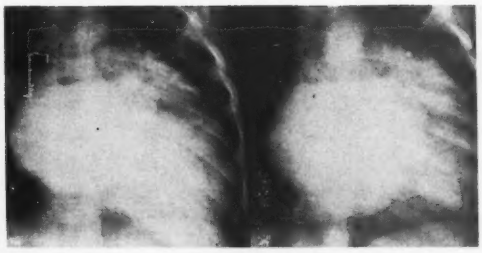

Figure 5

Case 1. Large left atrial volume changes during ventricular diastole (left) and ventricular systole (right).

Diastasis, the phase of diastole preceding atrial contraction, was definitely present in two of the three patients in whom a left atrial pressure pulse was obtained. This phase is absent in patients with mitral stenosis.[13] In children with rapid cardiac rates, however, diastasis could be masked.

In one patient the left ventricular end-diastolic pressure was elevated as seen in figure 1. The left ventricular end-diastolic pressure is reported as not being elevated in patients with acquired mitral insufficiency.[14] The "washing phenomenon" in which the catheter enters the left ventricle in diastole only to recoil back in the atrium with the regurgitant flow was observed in one patient.[14] The left ventricular pressure pulse showed a rapid fall during late ejection in three patients (fig. 1). This contour has been described by Davila[15] and is attributed to the inability of the ventricle to maintain ejection pressure during the period when regurgitant flow is maximal.

Pathologic Findings

Postmortem examination was performed on two patients. The autopsy on case 8 was car-

Table 3

Hemodynamic Findings, Right Heart Catheterization

Case	Right ventricular pressure S/D	Pulmonary artery pressure S/D	Pulmonary capillary wedge (M)	Wedge pressure pulse
1. LA	37/0	37/25	16	nonphasic
2. PP	40/0	42/24	—	—
3. CP	26/2	25/15	—	—
4. DP	44/0	44/14	18	elevation V wave
6. MB	62/0	60/25	20	elevation V wave
7. SE	80/0	—	—	—
8. MP	50/12	50/37	?32	elevation V wave
9. DW	38/0	35/25	20	nonphasic

ried out at a neighboring hospital. Gross findings consisted of enlargement of the left atrium and left ventricle, with a thickened, widely dilated mitral valve annulus. The chordae tendineae were short and appeared to restrict leaflet mobility. Microscopically there was evidence of endocardial sclerosis, primarily in the region of the mitral valve.

The second patient (case 7) died during ventriculotomy for repair of a ventricular septal defect. Examination showed the typical anatomic arrangement in corrected transposition of the great vessels, with the aorta arising anteriorly from the left ventricle and the pulmonary outflow tract arising medially

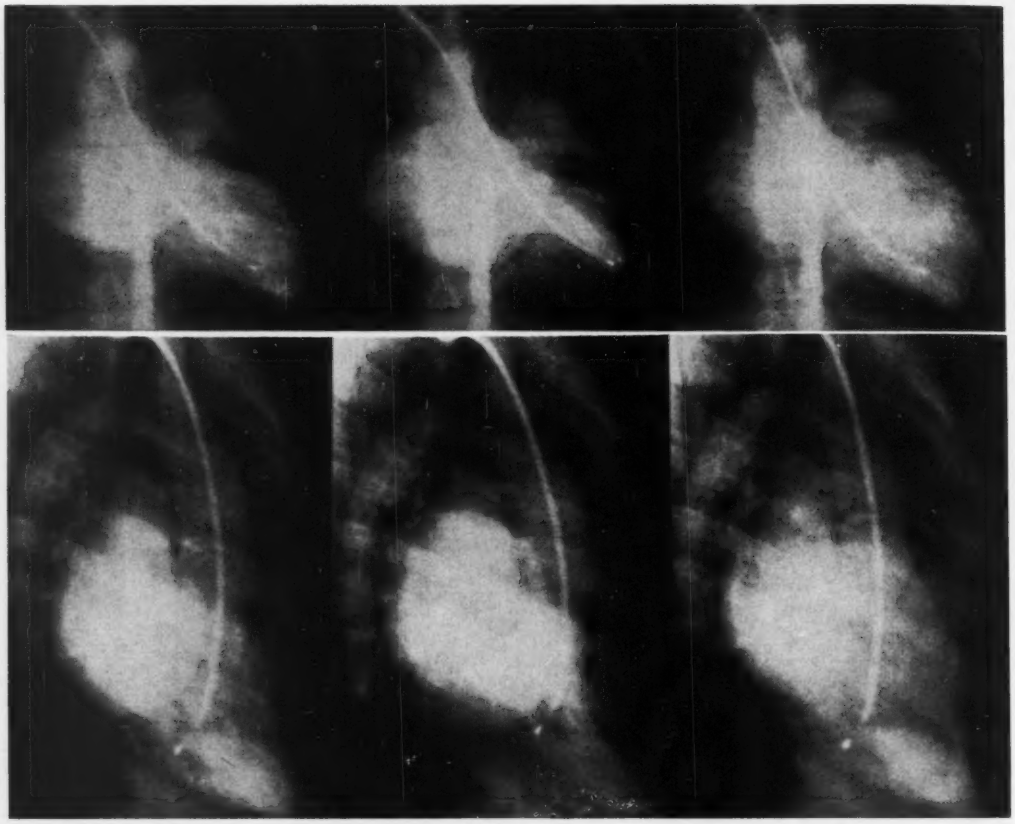

Figure 6

Case 10. Upper, posteroanterior view; lower, lateral view. Left ventricular angiogram during early systole (left), late systole (center), and diastole (right) showing marked regurgitation of contrast material into the left atrium. Note variation in left atrial volume during cardiac cycle.

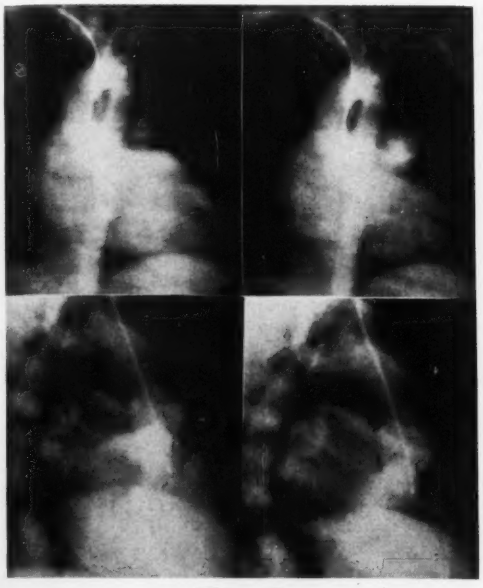

Figure 7

Case 5. Upper, posteroanterior view; lower, lateral view. Left ventricular angiogram showing regurgitation of contrast material into the left atrium. Left, diastole; right, systole.

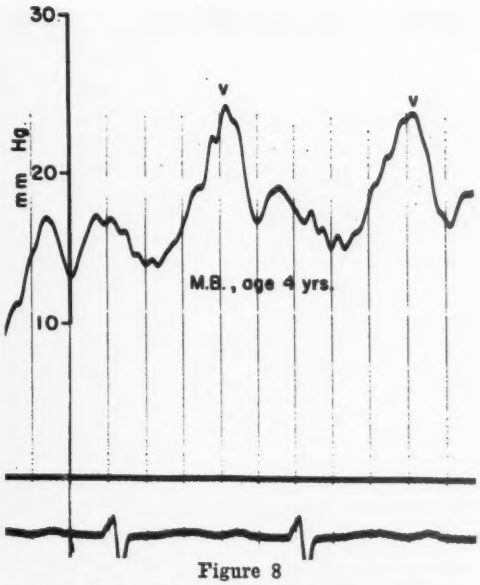

Figure 8

Case 6. Left atrial pressure pulse showing elevation of the V wave and a rapid y descent.

and somewhat posteriorly from the right ventricle. The left atrioventricular valve was tricuspid and markedly deformed. The valve leaflets were thickened, the chordae tendineae were shortened, and the annulus was dilated. There were dilatation and hypertrophy of the left atrium and ventricle. Several pinpoint openings were present in the ventricular septum, which was translucent. Microscopic examination of the small pulmonary vessels demonstrated vascular lesions consisting of medial hypertrophy and intimal thickening. This patient had marked elevation of pulmonary artery pressure. Vascular lesions have been reported in acquired mitral insufficiency by Becker et al.,[16] and may be attributed to increased pulmonary venous pressure and stasis.

Surgical Results

Six patients have had surgical repair of their defects. Repair of the insufficient mitral valve was carried out through a right posterolateral incision through the fifth intercostal

Table 4

Hemodynamic Findings, Left Heart Catheterization

Case	Left atrial mean pressure mm. Hg	V/A*	y/MLAP† (0.1)	Diastasis	Left ventricular pressure S/D mm. Hg
2. PP	26	2.5	.7	+	—
6. MB	19	1.5	.5	±	86/0
9. DW	25	2.0	.6	+	75/12
5. RJ		Retrograde left heart study			118/20
10. SB		Retrograde left heart study			115/0

*Ratio of the pressure at the peak of the V wave to the pressure at the peak of the A wave.
†Ratio of the y descent in the first 0.1 second to the mean left atrial pressure.

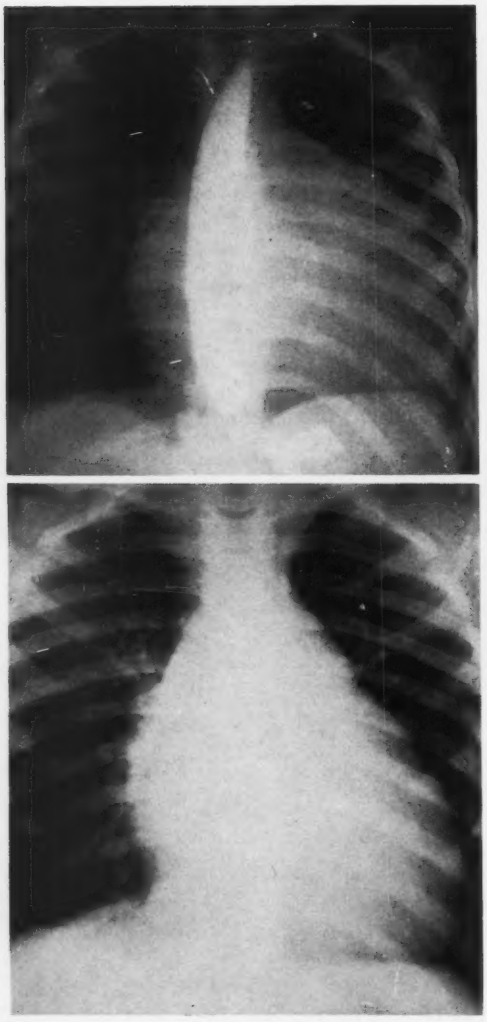

Figure 9

Case 1. Upper. Preoperative roentgenogram showing marked cardiac enlargement with a double atrial contour and considerable spreading of the mainstem bronchi. Lower. Postoperative roentgenogram (1 year) showing decrease in the over-all cardiac size, particularly of the left atrium and ventricle. The spreading of the bronchi is diminished.

space. The venae cavae and the right superficial femoral artery were cannulated. Extracorporeal circulation was accomplished with an apparatus employing roller pumps and a rotating-disk oxygenator. The mitral valve

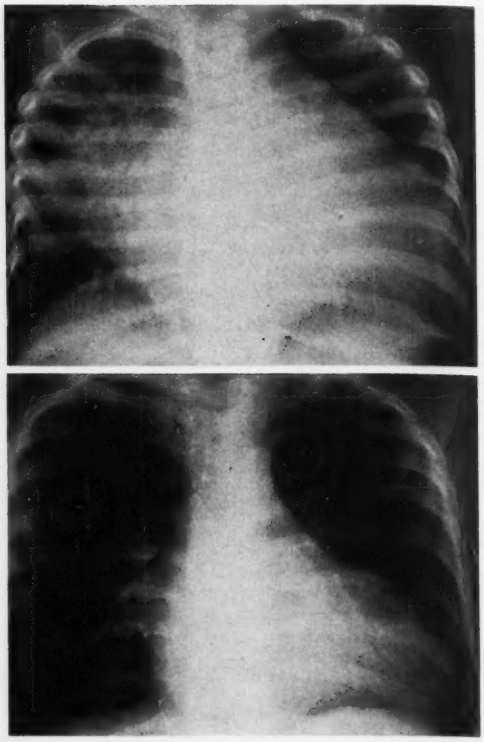

Figure 10

Case 2. Upper. Preoperative roentgenogram. The heart size is markedly increased. The left atrium is markedly dilated forming the right cardiac border. Lower. Postoperative roentgenogram (2 years). There has been a decrease in over-all cardiac size with diminished prominence of the left atrium.

was exposed through a longitudinal incision in the left atrium, which bulged markedly to the right in each patient. The mitral insufficiency was corrected by placing plication sutures of heavy silk through the mitral annulus at one or both commissures. In one patient a cleft of the anterior leaflet was sutured. The surgical findings and follow-up clinical and roentgenologic examinations are presented for each of the patients.

Case Histories

Case 1

This 5-year-old girl had been in severe congestive heart failure and was only slightly improved on a medical program. At the time of operation

the left atrium was found to be considerably enlarged. A regurgitant systolic jet was palpable over the left atrium. The annulus measured 4 to 5 cm. in greatest diameter. The mitral valve leaflets were somewhat thickened and the leaflets in the region of the posterior commissure seemed to lack proper chordal attachment, so that they flapped in the blood stream. The incompetence was materially reduced by plicating the annulus posteriorly with mattress sutures of 3-0 silk. Approximately one third of the length of the mitral valve was closed posteriorly. The patient tolerated the procedure quite well and the postoperative course was uneventful. From a clinical standpoint the girl was markedly improved.

Over 2 years later the patient was fully active, no longer receiving any cardiac medications and had a normal exercise tolerance. Physical findings consisted of minimal cardiomegaly with a soft apical pansystolic murmur. Roentgenograms reveal a marked decrease in cardiac size, less prominence of the left atrium and left ventricle, and diminished spreading of the bronchi (fig. 9).

Case 2

This 2-year-old boy had been observed since the age of 2 months with frequent respiratory tract infections, growth retardation, and two bouts of congestive heart failure. Surgical repair of his mitral valve lesion was undertaken because of increasing cardiac symptoms and progressive cardiomegaly, despite an intensive medical program. At operation the heart was found to be tremendously enlarged and the left atrium aneurysmally dilated. The mitral valve ring was widely dilated and the leaflets were thick and rubbery. The left atrial wall was increased in thickness and showed endocardial sclerosis microscopically. Regurgitation occurred in the region of the posterior portion of the valve, the leaflets being restricted by anomalous insertion of short, thickened chordae tendineae. Horizontal mattress sutures posteriorly across the annulus decreased the diameter of the mitral valve ring considerably. A small amount of insufficiency remained but additional suturing was thought unwise because of the risk of creating stenosis. The postoperative course was uneventful and during the subsequent 2-year period the boy has resumed a normal growth pattern, is no longer receiving cardiac medications, and has a normal exercise tolerance. Roentgenograms reveal a marked decrease in the over-all cardiac size, particularly of the left atrium and left ventricle (fig. 10).

Case 3

This 6-year-old girl was the least incapacitated of the group although there was ease of fatigue and growth retardation. At surgery the left atrium was enlarged and a systolic thrill was felt over it.

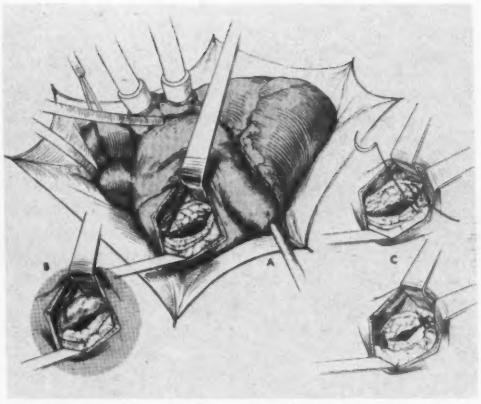

Figure 11

Illustration of the types of congenital malformation of the mitral valve encountered in this series. A. Retracted anterior leaflet with shortened chordae tendineae. B. Anomalous insertion of chordae tendineae with "overshoot" of the anterior leaflet. C. Repaired mitral valve with plication sutures across the annulus anteriorly and posteriorly.

The mitral valve appeared thickened and white, and a cleft of the anterior leaflet was noted and was closed with figure-of-eight sutures. The postoperative course was complicated by a prolonged febrile course, which was thought to be the postcardiotomy syndrome. A marked decrease in cardiac size has not been noted, and a residual murmur of mitral insufficiency has persisted in the subsequent year. The child has had an increase in exercise tolerance, has gained 6 pounds in weight, and appears to be progressing quite satisfactorily.

Case 4

This patient had correction of his defect at the age of 6 years. At surgery the left atrium was markedly dilated and a systolic thrill was felt over it. The aorta lay far to the left in the typical position of corrected transposition. The "mitral" valve was noted to be markedly incompetent. The annulus was widely dilated and the valve appeared to have three cusps. The valve leaflets were thickened and were bound down by shortened chordae tendineae. The "mitral" annulus was narrowed anteriorly and posteriorly by a series of horizontal mattress sutures. The amount of insufficiency was reduced dramatically.

The postoperative course was entirely satisfactory. A soft apical systolic and a diastolic murmur have persisted, despite marked clinical improvement. The boy is now fully active, attends school, and is not taking cardiac medications. Roentgenograms reveal a marked decrease in cardiac size.

Case 5

After repair of a coaretation of the aorta at age of 2 years in this boy, findings of mitral insufficiency persisted, symptoms continued and one bout of congestive heart failure occurred. The defect was repaired at age of 4 years. At surgery a tremendously enlarged left atrium was found, which pushed the right atrium into the superior vena cava anteriorly. A systolic thrill was felt in it. The mitral annulus was moderately dilated and the anterior leaflet did not approximate the posterior leaflet but appeared to overshoot it. The thickened anterior leaflet seemed to be attached by a few long chordae tendineae that allowed eversion of the leaflets during ventricular systole. The mitral valve annulus was reduced by horizontal mattress sutures through the anterior and posterior commissures. The valve then appeared to be completely competent. The procedure was tolerated quite well, and there were no postoperative complications. During his 6 months of follow-up there has been a marked increase in exercise tolerance, a 4-pound weight gain, and he has been taken off cardiac medications. Roentgenograms show a decrease in cardiac size, particularly of the left atrium and left ventricle.

Case 6

This boy was admitted at the age of 2½ years in severe congestive heart failure. At surgery a large left atrium was seen to bulge forward from a posterior position, and a systolic thrill was felt over it. The mitral valve annulus was widely dilated, the valve leaflets were thickened and white, and the chordae tendineae were shortened. The anterior leaflet seemed to lack proper chordal attachment at the midpoint. During left ventricular contraction the leaflets did not approximate. Horizontal mattress sutures across the mitral annulus anteriorly and posteriorly reduced the size of the annulus. The valve leaflets seemed to approximate much better and the valve opening was reduced to 1½ fingers. Postoperatively the patient did well although there was a residual, less intense systolic murmur at the apex. Since discharge he has gained 3 pounds and increased his activity but is still taking digitoxin. Roentgenograms reveal a considerable decrease in the over-all cardiac size, with diminution in the size of the left atrium and left ventricle.

Comment

All the patients who have had surgical repair of their mitral valve lesions were severely incapacitated preoperatively. Following the surgical procedure there has been a dramatic relief of symptoms in all patients and, with one exception, a remarkable decrease in cardiac size. The murmur of mitral incompetence has persisted but has diminished in intensity.

The types of malformations encountered in our series are shown in figure 11. Anomalous chordal insertion with regurgitation in the region of the posterior commissure appears to be the commonest. In one instance a cleft in the anterior leaflet was sutured. Recently Edwards[17] has called attention to the presence of accessory chordae tendineae in association with clefts of the anterior leaflets with partial and complete atrial ventricular canal. The question can be raised in the patient with the cleft of the anterior leaflet whether persistence of mitral insufficiency is related to the presence of accessory chordae that may continue to restrict leaflet mobility.

Summary

The clinical and hemodynamic findings in 10 patients with mitral insufficiency on a congenital basis are described.

Six of these patients have had repair of the defects with dramatic clinical improvement noted. The findings at the time of surgical repair have been summarized.

The severity of the symptoms and the benefits to be derived from surgical repair should encourage vigorous attempts to establish the correct diagnosis. This is best accomplished by either recording the typical left atrial pressure pulse of mitral insufficiency during left heart catheterization or by left ventricular angiography to demonstrate the regurgitation of contrast material into the left atrium.

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Sydenham was called "a man of many doubts" and therein lay the secret of his great strength.—Sir William Osler. *Aphorisms from His Bedside Teachings and Writings.* Edited by William Bennett Bean, M.D. New York, Henry Schuman, Inc., 1950, p. 112.

Aneurysms of the Previously Ligated Patent Ductus Arteriosus

By Richard S. Ross, M.D., Frederick P. Feder, M.D., and Frank C. Spencer, M.D.

PATENCY of the ductus arteriosus is, under most circumstances, a relatively benign condition. Surgical therapy has been available since 1938,[1] results are excellent, and the operative risk is small.[2-6] Recanalization of a ligated ductus arteriosus occasionally occurs and may be associated with the formation of an aneurysm. Recanalization and aneurysm formation are serious complications associated with sizable risks whether they are attacked surgically or allowed to remain untreated. These complications are presented in case 1 of this report. Four similar cases found in the records of The Johns Hopkins Hospital are also briefly abstracted here.[5, 7, 8] These five cases have been combined with 12 collected from the literature and are summarized in table 1.

Case Reports

Case 1

(J.H.H. 85 01 86): P. H., a white woman was known to have a heart murmur in childhood but was asymptomatic until age 21. At this time, during her first pregnancy, she noted swelling of her legs, feet, hands, and face, and developed mild dyspnea on exertion. She was treated for pre-eclampsia. After delivery her symptoms subsided, but she remained weak and tired easily.

At age 30, at another hospital, a patent ductus arteriosus was ligated with silk sutures. The patient developed a wound infection with *Staphylococcus aureus* that was "resistant" to penicillin but responded to treatment with Furadantin and chloramphenicol. Three weeks after operation, a faint continuous murmur was heard in the pulmonary area. Several examinations by her local physician after her return home revealed only a systolic murmur.

Six months after operation the patient developed chills and fever, and blood cultures were positive for *Staph. aureus,* again "resistant" to penicillin. She was treated for 5 weeks with streptomycin, dihydrostreptomycin, and chloramphenicol. During this illness, the attending physician heard a continuous murmur, whereas he had heard only a systolic murmur previously.

During the 4 years between the endarteritis and admission to this hospital, the patient was seen regularly by a cardiologist, who noted an increase in the size of the heart and persistence of a continuous murmur. The patient took prophylactic oral penicillin daily during these 4 years. Her only symptoms were mild dyspnea on exertion and occasional palpitations.

On admission to this hospital, 4½ years after the first operation, the pertinent findings were a blood pressure of 132/64 mm. Hg, an accentuation of the second heart sound in the pulmonary area, and a loud continuous murmur in the second left interspace. Calcium was present in the region of the pulmonary artery on chest roentgenogram, suggesting the possibility of aneurysm formation (fig. 1). Cardiac catheterization demonstrated a large left-to-right shunt in the pulmonary artery, but the pulmonary arterial pressure was normal.

At thoracotomy with hypothermia of 31 C. a 5-cm. aneurysm in the region of the ductus arteriosus was found and scar tissue on its anterior surface enveloped the vagus and phrenic nerves. A strong thrill was palpable over the aneurysm. The aneurysm was freed from the left bronchus and adjacent nerves by sharp dissection. Clamps were placed across the aorta above and below the aneurysm and obliquely across the left pulmonary artery. The aneurysm was then removed, and the openings in the aorta and pulmonary artery were sutured. The aorta was occluded for 10 minutes.

The aneurysm was 3 cm. in internal diameter. The sac had a 1-cm. communication with the aorta (fig. 2) and an 8-mm. communication with the pulmonary artery. One silk suture lay free in the lumen of the aneurysm. Microscopically the specimen revealed a scarred, thickened, hyalinized vessel wall with much chronic inflammation in the adventitia and a foreign-body reaction within the wall about the sutures.

The postoperative course was complicated by the development of loculated pleural effusions and

From the Departments of Medicine and Surgery, The Johns Hopkins Hospital, Baltimore, Maryland.

Aided by a grant from the Life Insurance Medical Research Fund.

fever. Approximately 1 month after operation the patient became afebrile and was discharged. One year after operation she was asymptomatic and living a normal life.

Case 2

(J.H.H. 54 53 73): A. E., a 5-year-old girl, had a 1.6-cm. ductus ligated with three silk pursestring sutures, one mattress suture, and a ligature of braided silk. Convalescence was uneventful, and at discharge 17 days after operation no diastolic murmur was heard. At 2 months and again at 5 months after operation respiratory infections were treated with penicillin by the family physician. The second of these febrile episodes persisted for 1 month, and during this illness a typical continuous murmur was heard. A single blood culture was sterile, but penicillin, aureomycin, and streptomycin were given for 3 weeks.

Seven months after operation, at the time of return to The Johns Hopkins Hospital, the patient was found to be chronically ill, and the typical physical findings of a patent ductus arteriosus were demonstrated. Blood cultures were positive for *Staphylococcus albus*. The patient was treated for 10 weeks with aureomycin, streptomycin, and chloramphenicol. Nine and one-half months after the initial operation, at re-exploration a large saccular aneurysm was found arising from the pulmonic end of the ductus. The aneurysm was mobilized and excised, but a tear in the aorta led to a fatal hemorrhage. The surgical specimen contained a thick vessel wall consisting of fibrinous clot, polymorphonuclear leukocytes, a few macrophages, and old suture material. In addition, postmortem examination revealed giant-cell granulomata in the lung, suggestive of fiber emboli, presumably from suture material.

Case 3

(J.H.H. 54 57 94): J. M., a white man, was first seen at age 18 for evaluation of congenital heart disease. Significant physical findings were a blood pressure of 115/65/0 mm. Hg, collapsing radial pulses, and a loud, continuous, machinery murmur, maximal in the pulmonary area.

At operation a short patent ductus arteriosus, 1.3 cm. in diameter, was occluded with silk pursestring sutures at the aortic and pulmonary ends and a single transfixion suture in between. The pulmonary arterial thrill was obliterated by this procedure. The postoperative course was benign. On examination 18 days after operation significant physical findings were a blood pressure of 112/88 mm. Hg and a faint but definite continuous murmur in the pulmonary area.

Examination 1 year after operation revealed an increase in the systolic component of the continuous murmur and a blood pressure of 120/65 mm. Hg. A diagnosis of recanalized ductus arteriosus was made but surgery was deferred. Three years after operation a grade-II continuous murmur was again heard in the pulmonary area and cardiac catheterization was carried out. The pulmonary blood flow was 4.5 times the systemic flow, and the pulmonary arterial pressure was 100/40 mm. Hg. Surgery was not advised because of the pulmonary hypertension. A second catheterization 5 years later showed no change in the pulmonary artery pressures, but the pulmonary flow had decreased to that of the systemic flow, indicating that there had been an increase in pulmonary vascular resistance during the 5 years between studies.

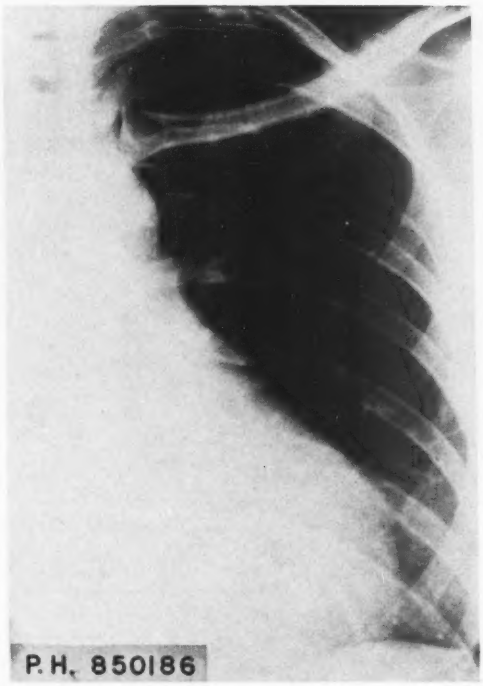


Figure 1

Chest x-ray, case 1. A faint ring of calcium can be seen in the region of the enlarged pulmonary artery.

At age 26, 8 years after the initial operation, re-exploration revealed an aneurysm measuring 1.5 cm. in diameter. The ductus was divided, and the aortic and pulmonary stumps were sutured; but when the aortic clamp was removed, moderate bleeding from the suture line was followed by myocardial failure and death.

Pathologic examination of the ductus revealed a calcified sac with hyaline walls and old hyaline mural thrombi on the anterior lateral surface of

Table 1

Aneurysm of the Ligated Ductus Arteriosus

Case report	Sex/age	First operation PDA size	Technic	When recanalized	Onset symptoms of bacterial endocarditis	Organism	X-ray diagnosis aneurysm	Subsequent operations
Case 1. P. H.	F 35	?	ligation; 3 ligatures	? 1 mo. 6 mo.	1 mo. 6 mo.	Staph. aureus	yes 4 yr.	excised
Case 2. A. E.	F 5	1.6 cm.	suture-ligation; 4 ligatures	5 mo.	2 mo.	Staph. albus	yes 6 mo.	excised; operative hemorrhage
Case 3. J. M.	M 18	1.3 cm.	suture-ligation; 3 ligatures	18 da.	——	——	no	excised; heart failure
Case 4. H. R.	F 23	1.2 cm.	suture-ligation: 5 ligatures	46 da.	46 da.	Staph. albus	no	excised
Case 5. T. M.	F 4	"large"	suture-ligation; 3 ligatures	15 da.	10 da.	Staph. aureus	yes 15 da.	excised
Jones *et al.*[9], case 3	F 13	?	ligation; 2 ligatures	33 da.	30 da.	Staph. aureus	yes 33 da.	——
Gerbauer[10]	— 18	?	ligation	? kept murmur	?	?	no	——
Tubbs[11] case 4	F 10	?	ligation	28 da.	pre-operative	Strep. viridans	no	——
Holman *et al.*[12], case 4	F 11	?	ligation, #1— 1 lig. #2— 3 lig.	 30 da. 42 da.	——	Staph. albus	no	#3-excised
Das *et al.*[13], case 1	F 25	?	ligation, 2 ligatures	105 da.	1 yr.	coag. neg. Staph.	yes 1 yr.	excised; loss of vagus and recurrent laryngeal nerves
Das *et al.*[13], case 2	F 5	.4 cm.	ligation, 2 ligatures	no diastolic murmur	——	——	yes 24 da.	excised; pneumonectomy to control hemorrhage
Servelle *et al.*[14]	— 7	.7 cm.	ligation, 4 ligatures	35 da.	29 da.	Staph. aureus	yes 38 da.	#2-endaneurysmorraphy #3-repeated to close leak
Kerwin *et al.*[15]	F 34	2.5 cm.	ligation, 4 ligatures	? diast. murmur only. Severe pulm. hypertension	——	——	yes 7 mo.	none
Lindskog *et al.*[16]	F 16	?	ligation, 3 ligatures	between 2 and 8 mo.	——	——	yes 8 mo.	excised
Crafoord[17]	F 22	4.6 x 3 cm.	division and suture	60-90 da.	pre-operative	gamma Strep.	no	excised
Humphreys[18], case 6	M 11	1.5 cm.	ligation, 2 ligatures	7 da.	——	——	?	none
Milstein *et al.*[19]	F 19	1 x 2.4 cm.	ligation	"some weeks"	?	?	?	excised

the ductus. A lung biopsy revealed multiple thrombi and recanalized thrombi in dilated vessels with dense hyaline walls.

Case 4

(J.H.H. 56 36 12): H. R., a white woman, was told she had a "bad heart" at age 2. The diagnosis of patent ductus arteriosus was made at age 23 on the basis of a typical continuous murmur and slight left ventricular enlargement. At thoracotomy a large ductus measuring 1.2 cm. in diameter was ligated with two silk pursestring sutures and three transfixion sutures.

Seven weeks later the patient had a dental extraction without prophylactic penicillin. Five days afterward she developed anorexia, fatigue, chills, and intermittent "dark urine."

On readmission, 10 weeks after operation, she appeared chronically ill with a temperature of 101.3 F. (rectal), a blood pressure of 120/55 mm. Hg, and a grade-II continuous murmur in the pulmonary area, accompanied by an accentuated second pulmonic sound and diastolic tap. Seven blood cultures were positive for hemolytic staphylococcus albus. Treatment was begun with

Result	Related pathology
living	
died at operation	fiber emboli in lungs
died at operation	pulmonary vascular sclerosis, pulmonary hypertension
living	
living	Staph. cultured from sutures
died (bacterial endocarditis)	sutures loose in wall of aneurysm
died	evidence of arteritis in aneurysm; recanalized
died (bacterial endocarditis)	loose sutures in aneurysm; pulmonary infarets
living	loose sutures in aneurysm; bilobed aneurysm
living	calcified aneurysm
living	recanalization demonstrated
living	loose sutures in lumen, culture Staph.; persistent bacterial endocarditis likely
died—hemoptysis	ruptured mycotic aneurysm of left pulm. artery; loose old ligatures with pulm. emboli; recanalized ductus arteriosus
living	
died	appeared to be infected hematoma between aorta and P. A.
died 1 yr. postoperative	
died 2 hr. postoperative	large false aneurysm, pulmonary hypertension

6.4 million units of penicillin with 2 Gm. of Benemid per day. The temperature was normal after the third day.

After 3 weeks of chemotherapy, a second thoracotomy was performed. The previous sutures were found in a small aneurysm immediately adjacent to the ductus. The surgeons noted that "it looked as if the sutures had cut through and been extruded and the ductus had reformed." Vegetations were found only at the pulmonic end and were sterile on a bacteriologic culture. The ductus was divided, the ends were sutured, and a flap of pericardium was interposed between

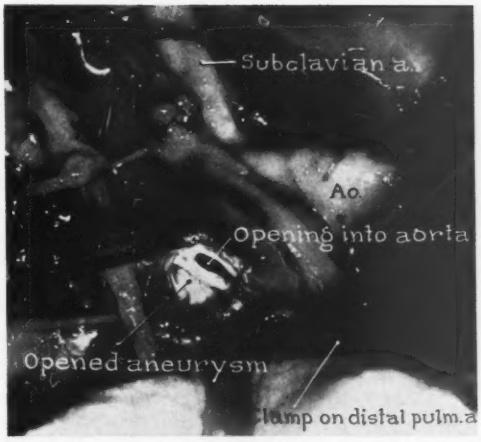


Figure 2

Relationships at operation in case 1. The aneurysm has been opened and its aortic opening is visualized.

the two suture lines. The patient was discharged on the twenty-third postoperative day and is asymptomatic and well at the present time, 8 years after the second operation.

Case 5

(J.H.H. 70 67 68): T. M., a 10-year-old white girl, was referred to The Johns Hopkins Hospital for surgical treatment of a patent ductus arteriosus. At operation a large, thick-walled, patent ductus arteriosus was exposed and closed by the suture-ligation technic. Pursestring sutures were placed at the aortic and pulmonic ends and a through-and-through mattress suture was placed between them. The thrill in the pulmonary artery was obliterated by the closure. Ten days later the temperature per rectum rose to 105 F.; blood cultures were positive for hemolytic staphylococcus aureus. Therapy was begun with six million units of penicillin intravenously and 1 Gm. of Benemid per day. An area of consolidation was observed in the left upper lung field near the mediastinum on a chest roentgenogram (fig. 3); it was thought to be either an aneurysm or an abscess. On the same day a faint continuous murmur was heard in the second left intercostal space. The continuous murmur increased in intensity and serial chest roentgenograms during the next 5 weeks showed a gradual increase in the opacity in the left upper lung field (figs. 4 and 5). An aneurysm of the ligated, recanalized, and presumably infected ductus was considered likely. After 7 weeks of intensive antibiotic therapy the patient still maintained a low-grade, intermittent fever.

At the second operation, exactly 2 months after

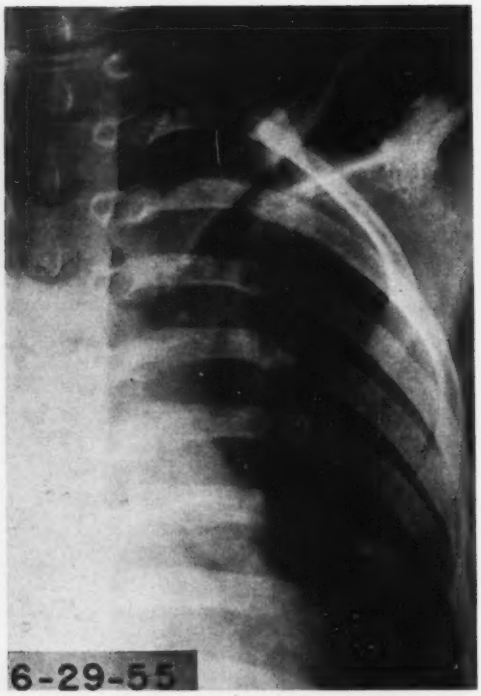


Figure 3

Chest x-ray, case 5, 3 weeks after the first operation reveals mass in left upper mediastinum.

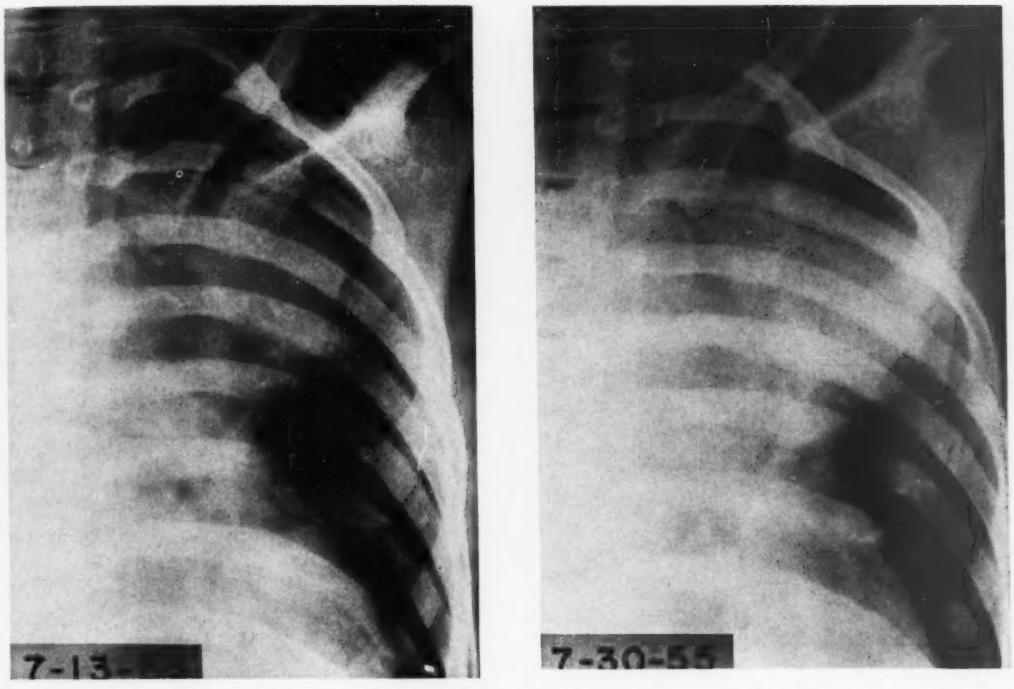
the first, a soft, pulsating aneurysm 8 cm. in diameter was found in the region of the ductus. The aorta and pulmonary artery were mobilized, the lung was dissected from the aneurysm, the aorta and pulmonary artery were cross-clamped, and the sac was incised. The three silk ligatures used in ligation were found within the wall of the sac. The aneurysm communicated with the aorta and pulmonary artery through 6-mm. openings. These openings were sutured and a flap of pericardium was interposed between them. *Staphylococcus aureus* was cultured from the ligatures found in the wall. Grossly, the cyst-like aneurysmal cavity was lined by a smooth, opaque membrane, free of vegetations. Microscopically the aneurysm wall showed smooth muscle and dense collagenous tissue. The intimal portion was composed of dense granulation tissue. Many plasma cells infiltrated all layers.

The postoperative course was uneventful and the chest roentgenogram 16 days after operation is shown in figure 6. When the patient returned 2 months after discharge, she was entirely asymptomatic. There was a soft, short systolic murmur over the pulmonary area and the heart size had decreased. Three years after operation she was living a normal life.

Discussion

The clinical features of postoperative aneurysms of the ductus arteriosus can be determined from inspection of table 1. The female preponderance in the 17 cases presented is consistent with the greater frequency of patent ductus arteriosus in women. Eleven of the aneurysms appeared in patients treated by simple ligation, five occurred after suture-ligation, and one after division. In the four cases treated at this hospital by the suture-ligation technic, the patent ductus was large, being 1.6, 1.3, and 1.2 cm. in diameter in three cases and probably larger than 1 cm. in the fourth. In the one case of aneurysm formation from a divided ductus, Crafoord's case, preoperative infection existed, and it was believed that the aneurysm originated from an infected hematoma between the aorta and pulmonary artery.[17] Recanalization seems to be essential to the formation of postoperative aneurysm and was present in all 17 cases. Recanalization apparently occurred at some time during the first 6 months after operation. This observation fits well with autopsy evidence that a ligated ductus arteriosus is converted into a fibrous cord with intima sealing the vessel at its ends within 1 year after operation.[4]

A ligated ductus arteriosus may become recanalized if the ligatures cut through the vessel wall, allowing re-establishment of its lumen. Such an area of suture transection could easily result in a hematoma and false aneurysm formation or serve as a site for bacterial growth. It has been suggested that post-stenotic dilatation of the ductus distal to a stenosing aortic end ligature may at times be responsible for true aneurysmal formation[12] Cruickshank,[20] in discussing the pathogensis of spontaneous aneurysms of the ductus arteriosus, stated that the aortic orifice was patent in all adult cases, suggesting that closure had occurred at the pulmonary end only, leaving the ductus open only at the aortic end, thus forming a cul-de-sac that was sub-



Figures 4 and 5

Chest x-rays, case 5, 5 weeks (left) and 8 weeks (right) after operations show progressive enlargement of the mediastinal mass.

ject to aneurysmal dilatation. A similar sequence of events would be possible with surgical closure if the pulmonary ligature was more effective than the aortic one in occluding the ductus. Recanalization could easily precede or accompany this process and the addition of infection could accelerate dilatation. It is known that the ductus becomes friable in the presence of pulmonary hypertension, which was present in case 3 and in the cases reported by Kerwin and Jaffe[15] and by Milstein and Brock,[19] and this condition may have contributed to the aneurysm formation.

Infection was present in 11 of the 17 cases. Bacterial endarteritis existed preoperatively in two cases and appeared after operation in nine cases. In six case reports no clinical or pathologic evidence of bacterial infection was described. In four of the nine patients with postoperative infection, evidence of infection antedated the appearance of signs, indicating that the ductus had recanalized. In three patients, recanalization and infection appear to have occurred simultaneously, and in one individual recanalization apparently preceded infection. Neither the onset of infection nor that of recanalization of the ductus can be dated precisely enough to permit conclusions regarding the causal relationship of these events. The absence of clinical and pathologic evidence for arteritis in six cases indicates that infection is not a sine qua non for aneurysmal formation. The two cases dying of bacterial endarteritis occurred in the prepenicillin era. In the eight postoperative infections in which an organism was cultured, Staphylococcus was invariably present. The arteritis in case 1 was probably cured by chemotherapy 4 years prior to the removal of the aneurysm, and no evidence of infection was found in the wall of the aneurysm. It is

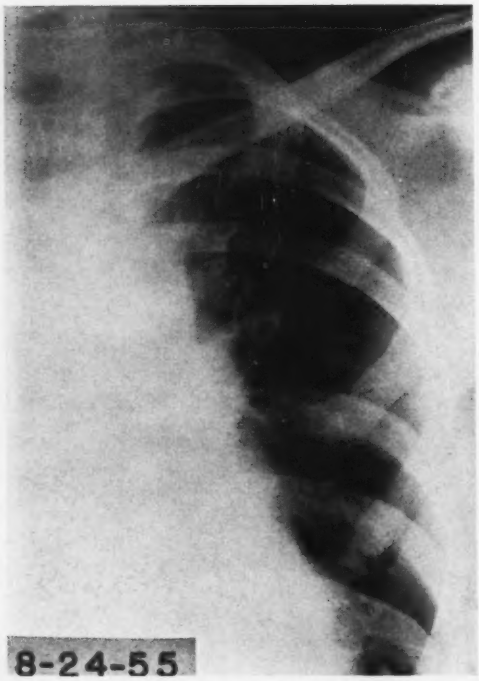


Figure 6

Chest x-ray, case 5, 16 days after excision of the aneurysm shows disappearance of mediastinal mass.

remarkable that a cure was possible in this case in view of the persistence of suture material in the wall of the aneurysm. The infecting organism was cultured from the old ligatures in case 5 even though blood cultures were sterile before surgery.

The high incidence of staphylococcal infections in these postoperative patients is in sharp contrast to the high incidence of streptococcus viridans infections on a simple patent ductus arteriosus. Eight of the nine cases of postoperative infection were known to be due to staphylococcus, and seven of these eight patients developed symptoms of bacteremia within 2 months of operation (mean time: 35 days). These facts suggest that the infection originated at operation and persisted because of contaminated ligatures, as postulated by Bahnson, Spencer, and Bennett.[7] The presence of a lag period between operation and evidence of bacteremia might be cited as an objection to this hypothesis; it is easy, however, to visualize a small, well-encapsulated suture abscess around a ductus remaining silent until a communication with the recanalized vessel lumen is established. The antibiotics prescribed in the postoperative period can be cited as a second explanation for the time elapsing between operation and clinical signs of sepsis. The persistence of infection, despite antibiotic therapy, can be attributed to the antibiotic "resistance" of the staphylococci and the potentiating effect of the foreign-body reaction about silk suture material. It is thought that the most likely source of infection in the cases of postoperative arteritis reviewed here is the inoculation of organisms on ligatures or the surgical field during operation.

The clinical picture in these cases was dictated by the presence or absence of infection. When the ductus aneurysm was infected, the typical syndrome of bacterial endarteritis on a patent ductus arteriosus was present. Clinical evidence of pulmonary embolization and infarction appeared in six of the 11 infected cases and in three of the six noninfected cases. In five infected cases and in one noninfected patient, suture material was found loosely attached to the interior of the aneurysm. Foreign-body granulomata, which may have originated from suture fiber emboli, were found in the lungs of three patients. If infection was not present, the clinical findings included murmurs suggesting recanalization and rarely massive hemoptysis and hoarseness. The presence of interscapular pain in case 1 may have been a direct symptom of the forming aneurysm. The clinical evidence for formation of an aneurysm is provided chiefly by x-ray. Pulmonary hypertension was present in case 3, in the case reported by Kerwin and Jaffe,[15] and in the case of Milstein and Brock.[19] The presence of an aneurysm was detected prior to death or operation in eight of the 17 cases. This was accomplished roentgenographically by the demonstration of a mass in the region of the ductus (fig. 3) or by finding calcific densities suggestive of an aneurysm (fig. 1).

The ductus aneurysm was successfully excised in seven patients and closed by the endaneurysmorrhaphy technic in another. The morbidity of the eight surviving patients included one emergency left pneumonectomy, the loss of the left vagus and left recurrent nerves in two cases, a possible persistent arteritis in one case, and loculated pleural effusions in one case. The mortality in these cases was 53 per cent. Three of the deaths occurred during or shortly after operation, two were due to persistent arteritis, one resulted from the rupture of a mycotic aneurysm of a pulmonary artery, and the cause is unspecified in three cases.

Summary

Five cases of postoperative aneurysm of the ductus arteriosus are presented and discussed, together with 12 from the literature. The ductus had become recanalized in all 17 patients. Infection was present in 11, having existed preoperatively in only two of these cases. The evidence suggests that contamination at the time of surgery was responsible for the infection in at least seven cases.

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Acute Hemorrhage and Necrosis of the Intestines Associated with Digitalization

By PETER C. GAZES, M.D., CHARLES R. HOLMES, M.D., VINCE MOSELEY, M.D., AND H. RAWLING PRATT-THOMAS, M.D.

ENTEROCOLITIS is a rather common entity seen often in a variety of forms by the clinician and the pathologist. There have been four reports of special types of gastrointestinal lesions in the patient with cardiovascular disease. Kleckner et al.[1] reported two cases of cardiac disease with acute pseudomembranous enterocolitis. Wilson and Qualheim[2] described a form of acute hemorrhagic enterocolitis afflicting chronically ill individuals. They considered this to be unlike acute pseudomembranous colitis. Seventeen of their 20 cases had chronic cardiovascular disease. Ende[3] described infarction of the bowel in cardiac failure in six cases. Recently, Katz[4] described a hemorrhagic duodenitis in myocardial infarction.

During the past 10 years we have observed, clinically and at autopsy, 10 cases of acute hemorrhage and necrosis of the bowel in patients with cardiac disease. In one additional case no autopsy was obtained but similar pathologic lesions were seen at laparotomy. Although the etiology is not apparent, it is of interest that all these patients had received large amounts of digitalis and several were in digitalis toxicity. Digitalization is considered as the main associated factor in these cases, especially since there was no mesenteric arterial involvement and only venous engorgement.

Case Reports

Case 1

A 72-year-old white man was admitted to the hospital because of syphilitic heart disease with congestive heart failure and atrial fibrillation. About 1 year earlier he began having dyspnea and took tincture of digitalis until one month before admission. In the hospital 0.3 Gm. of digitalis leaf was given daily for 13 days, a total of 3.9 Gm., in order to reduce the ventricular rate to 80. Subsequently, maintenance dosage was 0.2 Gm. daily. He had seven subsequent admissions in the next 1½ years for congestive heart failure and during the fourth admission was given an extra 0.5 mg. of digitoxin in addition to maintenance digitalis dosage. For 1 month prior to his last admission the patient had been taking 0.3 to 0.4 Gm. of digitalis leaf per day as he thought necessary for dyspnea. The day before admission he began to have some nausea and vomiting. The vomiting continued and 3 days later his abdomen became extremely tender with muscle guarding. An exploratory laparotomy was done because of the possibility of a mesenteric embolism or thrombosis. The entire small bowel beginning at the ligament of Trietz, cecum, and colon were dark and appeared nonviable. Sixteen hours later the patient died.

Case 2

A 58-year-old Negro was admitted to the hospital because of syphilitic heart disease with congestive failure. He was taking digitoxin, 0.2 mg. twice per day, for an unknown length of time. On the second day after admission 0.3 Gm. of digitalis leaf was begun daily and was continued until death. An electrocardiogram revealed second-degree atrioventricular block. On the fourth hospital day the patient complained of epigastric pain and passed a tarry stool. At this time his blood pressure was 188/70 and the hemoglobin was 9 Gm. per cent. Tarry stools continued until death 4 days later.

Case 3

A 66-year-old Negro woman was admitted to the hospital because of hypertensive cardiovascular disease with congestive failure. She was digitalized with a total of 2 Gm. of digitalis leaf and maintained on 0.1 Gm. daily. The patient was readmitted 11 months later because of congestive failure. During the first 24 hours of this period she was given 1.2 Gm. of digitalis leaf and subsequently 0.2 Gm. daily along with mercurial diuretics. About 2 weeks later, premature beats were noted and 3 days later an electrocardiogram re-

From the Departments of Medicine, Pharmacology, and Pathology, Medical College of South Carolina, Charleston, South Carolina.

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vealed premature ventricular beats as trigeminy and first-degree atrioventricular block. Nausea developed, and the digitalis was stopped. Five days later she was compensated but began to have abdominal pain with marked tenderness. Abdominal tenderness was still present 24 hours later and the blood pressure was stable at 120/80. A few hours later she vomited blood and died.

Case 4

A 62-year-old white man was admitted to the hospital because of hypertensive cardiovascular disease with congestive failure. He had intermittent episodes of congestive failure for 4 years and was taking 0.1 Gm. of digitalis daily. On this admission 0.5 Gm. of digitalis leaf was given and then 0.2 Gm. daily. The patient was readmitted 11 months later because of congestive failure and received 0.2 Gm. of digitalis leaf daily for 11 days when it was increased to 0.3 Gm. per day. Also, at this time 4 ml. of digalen were given intramuscularly because of rapid atrial fibrillation. Two days later digitoxin 0.3 mg. was given and continued daily until death. He became compensated and his ventricular rate slowed to 86 beats per minute. Six weeks later, however, he had a profuse liquid black stool and complained of lower abdominal pain. The blood pressure remained at a level of 220/110 and the hemoglobin was 14 Gm. per cent. A week later the patient began to vomit and complained of epigastric pain. Nausea and vomiting continued for 3 days until he died after a hematemesis.

Case 5

A 71-year-old Negro man was admitted to the hospital in congestive heart failure with a diagnosis of hypertensive cardiovascular disease. He received 1.6 Gm. of digitalis leaf and was maintained with 0.1 Gm. daily. The patient was readmitted to the hospital 20 months later and the digitalis was increased to 0.2 Gm. per day. Subsequently digoxin, 0.25 mg. twice per day, was given instead of digitalis leaf. He was readmitted 2½ years later because of an injury to his right leg of 1 month's duration. He appeared to be compensated and was maintained on 0.2 Gm. of digitalis leaf per day. After 2 weeks he developed extreme generalized abdominal tenderness and voluntary rigidity with active peristalsis and died several hours later.

Case 6

An 81-year-old white woman was admitted to the hospital because of arteriosclerotic heart disease with congestive heart failure. She had been digitalized previously and was on maintenance dosage and metcaptomerin (Thiomerin) 2 ml. intramuscularly per week. Two days prior to admission she began to have nausea and vomiting. The electrocardiogram revealed left ventricular hypertrophy, ST-T changes of digitalis, and ventricular bigeminy. The vomiting continued over a 24-hour period with vague generalized abdominal pain and tenderness and slight distention. Digitalis was discontinued, and a Levine tube was passed. Forty-eight hours after admission she suddenly became unconscious, developed a very irregular rhythm, and died.

Case 7

A 55-year-old Negro woman was admitted to the hospital with a cerebral vascular accident and rapid atrial fibrillation. She received a total of 2 mg. of lanatoside C (Cedilanid) intravenously over an 8-hour period with a slowing of the ventricular rate from 180 to 120. In spite of supportive therapy she weakened rapidly and died 10 hours after admission.

Case 8

A 72-year-old white man was admitted to the hospital because of arteriosclerotic heart disease with congestive heart failure. For 2 years prior to admission he had intermittent episodes of congestive failure requiring increases in his maintenance digitalis and diuretics. The day prior to admission an additional 1 mg. of digoxin was given and maintenance was started of digitalis leaf, 0.2 Gm. daily. While in the hospital the patient received diuretics, 2 ml., and potassium solution three times per day. Episodes of sudden dyspnea and cough occurred and anticoagulation was started because of the possibility of pulmonary emboli. After 1 week he began to have epigastric pain, which gradually increased with generalized abdominal tenderness. He progressively weakened and died 2 days later.

Case 9

A 68-year-old Negro woman was admitted to the hospital because of hypertensive arteriosclerotic heart disease with congestive heart failure. Three days prior to admission she was given gitalin 2.5 mg. followed with 0.75 mg. every 6 hours for six doses, with a maintenance of 0.5 mg. daily. She also was receiving chlorothiazide, 500 mg. daily. The first day in the hospital 1 mg. of gitalin was given and subsequently 0.1 Gm. of digitalis leaf daily. On admission the patient complained of mild nausea and anorexia. An electrocardiogram revealed first-degree atrioventricular block with periods of complete block. The following day the nausea and anorexia became worse and she had vague abdominal pain. At this time the electrocardiogram revealed atrioventricular dissociation with interference beats. She passed several bloody stools and had some drop in blood pressure but did not develop shock. The abdominal pain increased and bright red blood was passed through

a gastric tube. The blood pressure gradually fell and she died 3 days later.

Case 10

A 75-year-old white woman weighing about 70 pounds was admitted to the hospital with arteriosclerotic heart disease and digitalis toxicity. She had dyspnea for about 6 months prior to admission. Each attempt at digitalization produced nausea. Two weeks prior to death she was given digitoxin, 0.2 mg. twice per day, for 1 week then 0.2 mg. daily. She also took Trilafon, which prevented nausea, and 500 mg. of chlorothiazide daily. A few days prior to admission an electrocardiogram showed first-degree atrioventricular block and there was no evidence of heart failure. Admission was necessary because of nausea, vomiting, rapid heart beat, and lower left abdominal pain. The patient was found to be compensated with a blood pressure of 150/90, and there was some tenderness over the left lower quadrant. An electrocardiogram revealed long runs of ventricular tachycardia. She was given 40 mEq. of potassium chloride and 500 ml. of glucose in water with clearing of the ventricular tachycardia and appearance of atrial fibrillation. Over 24 hours the abdominal pain became worse and the blood pressure gradually dropped. She became distended and had marked tenderness in the left lower abdominal quadrant and absent peristalsis. Laparotomy was performed because of the possibility of a mesenteric embolism. The small bowel and entire colon were discolored and appeared to be in varying stages of gangrene. The ileocecal area was involved most. The stomach was normal and the mesenteric arteries appeared patent. The mesenteric veins were congested and thrombosed at the junction of the venules to the bowel. A few hours after surgery the patient died. No autopsy was obtained.

Case 11

A 60-year-old Negro woman was admitted to the hospital because of arteriosclerotic heart disease and digitalis toxicity. She was digitalized about 5 years prior to admission and subsequently took 0.1 Gm. of digitalis leaf a day. During the past few months she increased this to twice a day and began to have nausea and vomiting 1 week prior to admission. On admission an electrocardiogram revealed first-degree atrioventricular block and periods of atrioventricular dissociation. The patient appeared compensated and was given intravenous fluids and oral potassium salts. Epigastric pain was noted on the day of admission. Digitalis was resumed at a dose of 0.1 Gm. daily, 3 days after admission. Two days later the abdominal pain became more severe and she gradually became distended with generalized tenderness, rebound tenderness, and hypoactive peristalsis. Mesenteric thrombosis was considered, and laparotomy was performed. During this procedure her blood pressure dropped and she required *l*-arterenol. At surgery, the entire large bowel was discolored greenish black, it contained hemorrhagic material, and its walls were friable. The entire jejunum, colon, and ileum, except for a central five feet, were similarly discolored. All of the bowel was edematous. There was no evidence of mesenteric thrombosis. Extensive resection of involved areas was performed, but the patient died 2 hours later.

Comment

The common denominator in these cases was digitalization with definite digitalis toxicity in seven. All these cases were autopsied except case 10, in which the abdomen was explored. The intestinal lesions resembled those described by Wilson and Qualheim[2] and by Ende.[3]

Grossly the intestine is described characteristically as showing marked venous engorgement with hemorrhage and edema of the wall. In the most heavily implicated areas it is purplish or reddish black. These changes are likely to be described as gangrenous by the surgeon or by the pathologist. In the strict sense it is not gangrene, since there is usually very little inflammatory reaction and no massive infarction. There is epithelial devitalization, and in cases that live for a sufficient length of time mucosal necrosis, ulceration, and secondary infection will supervene. The darkening of the intestine is due to the profound venous engorgement (fig. 1), which may be further intensified by blood in the lumen and mucosa. In eight cases there was blood in the lumen of the bowel. The intestinal wall is commonly friable.

Careful dissection of the mesenteric arterial system revealed no instance of thrombosis. In only one instance was there a significant degree of mesenteric arteriosclerosis, and this did not severely compromise the lumen. Venous thrombi were occasionally observed. In two cases thrombi were present at the mesenteric-enteric junction, but were obviously very recent and secondary to the venous stasis. Thrombi occurred in a few other instances but were related to inflammation and ulceration.

Microscopically the most conspicuous feature is the profound degree of venous engorgement, which is most evident in the submucosa, (fig. 2). Hemorrhage into the mucosa and edema of the submucosa are constant findings.

The gastrointestinal tract in this condition is not uniformly involved and most commonly shows a segmental or patchy distribution. The stomach was involved in only three instances and seldom to the degree observed in the intestine. Gastric ulcers were present in two others. Some portion of the small intestine was implicated in all instances and the degree of involvement was usually extensive. In four cases the entire small intestine showed conspicuous edema, congestion, and hemorrhage. In two, the ileum was the only portion of the small intestine affected. In one case the vascular engorgement was limited to the jejunum, and in three others various combinations of involvement of the duodenum, jejunum, and ileum were observed. It was remarkable that an uninvolved segment of intestine could occur with massive changes in the contiguous bowel. In four patients the entire colon showed congestive and hemorrhagic phenomena. In one there was no change in the large bowel. Patchy involvement of the colon occurred in the other five cases and in two of these the process did not extend beyond the cecum.

Six of the cases were judged pathologically to be in congestive failure. The presence of failure was based on peripheral edema, excess fluid in the serous cavities, pulmonary edema, and chronic passive congestion of the liver. The liver revealed chronic passive congestion in three cases, sinusoidal congestion in four cases, and no abnormality in four. Those with chronic passive congestion had definite digitalis toxicity.

Discussion

Kleckner et al.[1] considered their cardiac cases to have acute pseudomembranous enterocolitis. This form of enterocolitis has been reported in a variety of other situations, such as after surgery, during antibiotic therapy, with shock, and with staphylococcal infections. Wilson and Qualheim[2] described in 17 cases of chronic cardiovascular disease a form of acute hemorrhagic enterocolitis that they considered to be unlike the acute pseudomembranous type. Their cases were very similar pathologically to those described in this paper. The only common denominator noted by the authors was cardiovascular disease with congestive failure. They mentioned that "the temporal relationship to vigorous therapy for heart failure with digitalis or digitoxin and with mercurial diuretic agents is striking in many instances, and it is tempting to ascribe causal relationship to any one of these agents." Ende[3] was of the opinion that infarction of the bowel can occur with severe cardiac failure in the presence of insignificant vascular disease of the mesenteric vessels. He encountered this in six cases and described in detail the three most severe ones. In the milder cases, various segments of small bowel were hemorrhagic and the lumen contained frank blood. He believed that these changes represented mild pathologic changes associated with severe cardiac failure by contrast with the much more serious lesion of infarction of the bowel. It was postulated that severe cardiac failure, perhaps aided by vascular spasm, can produce ischemia severe enough to lead to infarction.

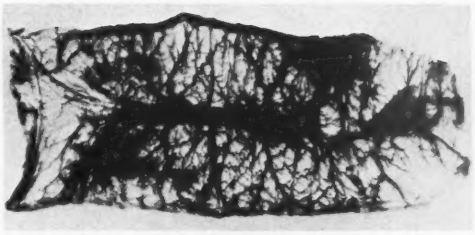

Figure 1

Transilluminated segment of small intestine showing profound venous engorgement with areas of mucosal hemorrhage.

Wilson and Qualheim[2] mentioned that the liver was chronically congested in one case but did not mention the hepatic status in the others. They did not mention whether or not mesenteric vein congestion was present nor did they note the digitalization status

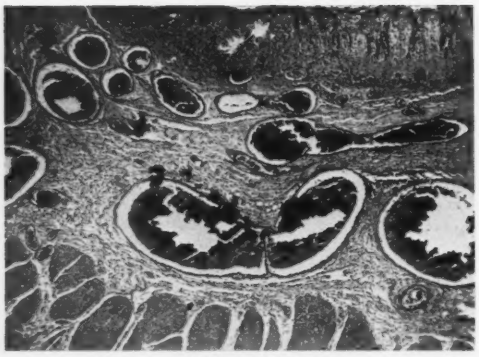

Figure 2

Distended veins in the edematous submucosa of the intestine. Mucosal hemorrhage is apparent in the upper left. Note the absence of inflammatory reaction.

of the patients. Ende[3] mentioned liver congestion in only one of his patients and in another that the blood vessels of the mesentery of the bowel had evidence of congestion but no thrombi. The first of his cases was given digitalis and mercurials but the amounts were not mentioned. A run of ventricular tachycardia occurred in this case. The second case had atrial fibrillation and ventricular bigeminy and was given diuretics and potassium chloride but the amount of digitalis was not stated. The third case had first-degree heart block and was on digitoxin, 0.2 mg. daily.

Portal Congestion Associated with Digitalization in Experimental Conditions

In view of the considerable experimentation and discussion related to the effects of digitalis glycosides on the liver and portal system, it is possible an extracardiac action of digitalis, especially in overdosage, produces pooling of blood in the splanchnic venous system.

In 1932 Bauer et al.[5] concluded from work on isolated perfused livers that there was a "sluice or sphincter mechanism" in the livers of dogs. The sphincter mechanism was located near the caval orifices of the main hepatic veins. Epinephrine opened and histamine closed the sluice while both drugs appeared to exert a weak constrictive action on the deeper veins. Specific localization of hepatic sphincters and their dynamic role in circulatory adjustments have been reviewed at length by Knisely and associates.[6, 7] Dock and Tainter[8, 9] particularly formulated the interpretation that digitalis, in addition to its cardiac effect, acts to reduce active circulating blood volume by pooling blood in the splanchnic area through constrictive effects in the hepatic veins. Their experimental observations were supported by those of Katz and associates[10] and, to some degree, by those of Nadler and associates,[11] although the latter were led to question the significance of this extracardiac action of digitalis. McMichael and Sharpey-Schafer[12] considered that digitalis may produce its immediate beneficial effect by lowering of the venous pressure, which could be on a basis of constriction of the portal venules in the liver. Thomas and Essex[13] demonstrated that spasm of the hepatic vein could be produced by anaphylactic shock, histamine, digitoxin, hydatid cyst fluid, and anoxia. Eddleman et al.[14] studied the effect of oral digitoxin in 12 normal subjects with the use of the electrokymograph and concluded that it acts to decrease the volume of blood returned to the heart and to increase force of cardiac contraction. More recently, Cotten and associates have used current methods to measure the effects of cardiac glycosides in reducing venous return and cardiac output[15] in the absence of important changes in total plasma volume or extracellular water.[16] These various hemodynamic studies offer indirect but highly suggestive evidence that digitalis exerts constrictive effects in the liver or hepatic vein structures. Such effects presumably can occur to a marked degree with excessive digitalization. Hueper and Ichiniowski[17] found marked congestion and engorgement of the liver with areas of necrosis, hyalinization, and edema in animals poisoned with digitalis leaf.

Clinical Considerations

Congestive failure, especially when chronic in nature, can be an additive factor with overdigitalization. At autopsy, however, four of our cases did not manifest congestive failure and many were clinically compensated

when they developed abdominal symptoms. If congestive failure were the sole cause, then we would expect to see this bowel syndrome more often. Only one of our patients, case 8, had received an anticoagulant, and the prothrombin times in this case were in a satisfactory range. Friedman et al.[18] demonstrated in dogs that during hemorrhagic shock or administration of epinephrine, constriction of the portal and hepatic veins occurred. Because of the sustained intrahepatic resistance, intestinal hemorrhage and even hemoperitoneum eventually occurred. In our cases there was no evidence of shock prior to or during this syndrome. Five patients had received a mercurial diuretic but this has been discounted as a factor.

This syndrome can be suspected when a patient develops abdominal pain while receiving large amounts of digitalis; unnecessary surgery thus may be avoided. Frequently a diagnosis of mesenteric thrombosis or embolism is suggested. Abdominal examination and flat plates do not reveal any characteristic diagnostic feature. It is well to stress again, especially with the advent of so many new preparations, that patients should be digitalized with caution. The antiemetic tranquilizer drugs are often given during digitalization, and so the early nausea of digitalis toxicity may be masked, as occurred in case 10. Also, maintenance digitalis alone can produce toxicity in the presence of potassium loss, such as occurs with diuretics and steroids.

Summary

Eleven cases with acute hemorrhage and necrosis of the bowel are described. In all cases there was high dosage of digitalis and definite toxicity in seven. Digitalis was considered as the main associated factor, especially since there was no mesenteric arterial involvement and, in four cases, there was no congestive failure at autopsy. Hepatic vein or sinusoidal sphincter constriction with resulting portal splanchnic venous congestion was considered as possible mechanisms by which digitalization produced this syndrome.

Acknowledgment

We wish to express our appreciation to Dr. Robert Walton for reviewing this manuscript.

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I made a bladder very supple by wetting of it, and then cut off so much of the neck as would make a hole wide enough for the biggest end of the largest fosset to enter, to which the bladder was bound fast. The bladder and fosset contained 74 cubick inches. Having blown up the bladder, I put the small end of the fosset into my mouth: and at the same time pinched my nostrils close, that no air might pass that way, so that I could only breathe to and fro the air contained in the bladder. In less than half a minute I found a considerable difficulty in breathing, and was forced after that to fetch my breath very fast; and at the end of the minute, the suffocating uneasiness was so great, that I was forced to take away the bladder from my mouth. Towards the end of the minute the bladder was become so flaccid, that I could now blow it above half full with the greatest expiration that I could make.—STEPHEN HALES, B.D., F.R.S. *Vegetable Statics,* 1727.

Myocardial Response to Cigarette Smoking in Normal Subjects and Patients with Coronary Disease

By T. J. Regan, M.D., M. J. Frank, M.D., J. F. McGinty, M.D., E. Zobl, M.D., H. K. Hellems, M.D., and R. J. Bing, M.D.

THE NEUROHUMORAL RESPONSES elicited by cigarette smoking[1] might be expected to affect the heart in a complex manner. Nicotine, the principal pharmacologic substance in tobacco has distinct effects upon the central nervous system,[2] and peripheral ganglia,[3] and is capable of stimulating the release of epinephrine[4] and antidiuretic hormones.[5] In view of these multiple factors which may variably modify myocardial oxygen consumption, the actual effect upon oxygen uptake of the heart may become less predictable than if one variable were altered.

The difficulty in determining the influence of cigarette smoking upon the human myocardium in terms of the work involved and energy released is that the currently available method for assessing myocardial blood flow and oxygen usage in man requires the presence of a steady state. Thus, the initial acute changes and possible phasic responses become difficult to assess. In a previous study the early response to cigarette smoking was associated with enhanced myocardial blood flow in normal subjects.[6] Whether a similar situation occurs after the known peripheral hemodynamic responses[1] have been established and maintained is examined in this investigation. To assess the potential role of tobacco as a cause of myocardial ischemia, the response to smoking in patients with coronary artery disease has been contrasted with that occurring in control subjects.

From the Department of Medicine, Wayne State University, College of Medicine, Detroit, Michigan.

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Procedure and Methods

The eight subjects with coronary artery disease of this study had incurred an acute myocardial infarction at least 1 year previously. This diagnosis was based on the clinical course and electrocardiograms. In addition all but one experienced angina pectoris. Cardiomegaly was not found on x-ray examination and diastolic hypertension above 95 mm. Hg was absent at the time of study. Six control subjects were studied who had recovered from acute benign illnesses. All the patients were habitual smokers.

The same experimental procedure was followed in both groups. After an overnight fast, the patient was premedicated with pentobarbital, 1 Gm. The coronary sinus and right atrium were catheterized and a needle was placed in the brachial artery. Coronary blood flow was determined in the recumbent position by the nitrous oxide desaturation technic[7, 8] followed immediately by a Fick cardiac output.

After the resting coronary flow and systemic hemodynamic determinations the patient began cigarette inhalation at 45-second intervals. Two cigarettes of a standard nonfilter brand were consumed in about 25 minutes, so that the initial increase of pulse rate and pressure was largely maintained during the subsequent 12 minutes of nitrous oxide inhalation. Upon cessation of inhalation, cigarette smoking was resumed at the same rate and was maintained throughout the coronary blood flow sampling. Heart rate, arterial pressure, and a left ventricular lead were monitored throughout the smoking, and were relatively constant during this procedure. In the tables are shown the values during the third minute of the coronary blood flow determination.

Results

Tabulation of the data of the control group has been made in table 1 and of the coronary group in table 2. During cigarette smoking both the control and coronary groups had significant acceleration of heart rate. A uniform rise in arterial pressure was seen in the former and with one exception, in the coronary group. Further, there was a tendency

Table 1

Cardiovascular Effects of Cigarette Smoking in Control Subjects

Initial	Age	Sex	B.S.A.		Coronary blood flow ml./100 Gm./min.	Myocardial: Oxygen arteriovenous difference vol. %	Myocardial: Oxygen consumption ml./100 Gm./min.	Total body oxygen consumption ml./min.	Cardiac index L./min./M.²	Pulse rate	Mean arterial pressure mm. Hg.	Left ventricular work Kg./M./min. per M.²	Ratio left ventricular work / Oxygen consumption (ml./Gm./min.)
R. L.,	40	M,	1.91	C*	85	11.80	10.06	271	3.25	84	80	7.14	0.71
				S†	75	11.01	8.23	289	3.81	88	84	8.34	1.01
L. P.,	34	M,	2.01	C	85	9.92	8.43	237	2.93	62	85	7.18	0.85
				S	95	9.80	9.31	218	3.69	68	90	9.58	1.03
J. A.,	36	M,	1.88	C	60	11.54	8.96	187	2.94	69	83	4.26	0.48
				S	65	10.98	7.12	188	3.16	73	90	5.26	0.74
H. S.,	44	M,	1.73	C	81	10.58	8.52	224	2.60	83	95	6.14	0.72
				S	88	10.94	9.65	194	2.88	87	108	7.68	0.80
D. L.,	48	F,	1.76	C	90	12.18	11.02	224	3.38	87	100	7.74	0.70
				S	102	10.62	10.81	224	3.56	93	110	8.98	0.83
L. M.,	36	M,	1.9	C	65	12.49	8.12	175	2.56	62	93	5.21	0.64
				S	74	13.09	9.67	193	3.05	76	95	6.62	0.68
Mean values				C	78	11.42	9.19	220	2.94	75	89	6.28	0.68
				S	83	11.07	9.13	218	3.36	81	96	7.74	0.85
p values					‡	‡	‡	‡	<0.01	<0.02	<0.05	<0.05	<0.05

*Control values.

†Data obtained during smoking.

‡No significant difference between control and smoking data.

for these hemodynamic changes to be more pronounced in the coronary group. All control subjects had an increase in cardiac index as did the coronary group, except for patients L. S. and F. N. The low values before smoking in the latter group are probably accounted for by their prior loss of functioning heart muscle. A uniform increment of left ventricular work during smoking was also more pronounced in the coronary group.

The attendant changes in coronary blood flow were not significant in either group. This phenomenon, combined with an unaltered myocardial oxygen extraction, resulted in a virtually identical myocardial oxygen usage as in the control state. The value before smoking of 8.63 ml. per 100 Gm. per minute in the coronary subjects was slightly less than that found in the control subjects, and its relation to the lower cardiac index remains speculative. In view of the relevance of myocardial usage of oxygen to the symptomatology of coronary artery disease, the relationship of left ventricular work to its oxygen consumption has been expressed as a ratio. The unknown variable of left ventricular weight precludes estimation of total left heart oxygen consumption in a given subject, but the identity of weights before and during smoking permits comparison of these two measures in a given patient. The distinct increment of left ventricular work in the presence of an unchanged myocardial oxygen consumption was reflected by a rise in this ratio of similar magnitude for both groups. This disproportion was not attended by anginal symptomatology or electrocardiographic evidence of ischemia in the patients with myocardial infarction.

Discussion

The experimental conditions of this study were limited to evaluation of the sustained effects of cigarette smoking upon the myocardium of man after the peripheral hemodynamic changes had become well established. Consequently, interpretation of the data cannot be applied without reservation to the acute changes occurring immediately after

Table 2

Cardiovascular Effects of Cigarette Smoking in Coronary Subjects

Initial	Age	Sex	B.S.A.		Myocardial: Coronary blood flow ml./100 Gm./min.	Myocardial: Oxygen arteriovenous difference vol. %	Myocardial: Oxygen consumption ml./100 Gm./min.	Total body oxygen consumption ml./min.	Cardiac index L./min./M.²	Pulse rate	Mean arterial pressure mm. Hg	Left ventricular work Kg./M./min. per M.²	Ratio left ventricular work / Oxygen consumption (ml./Gm./min.)
J. F.,	46	M,	2.07	C*82	13.88	11.38	272	2.29	99	85	5.77	0.51
				S†71	13.49	9.94	294	2.50	110	80	5.92	0.60
S. K.,	58	M,	1.82	C 60	11.23	6.73	165	1.78	73	83	3.86	0.57
				S 61	11.59	7.04	208	2.10	86	100	5.48	0.73
W. T.,	53	M,	2.01	C 90	10.70	9.58	286	3.18	82	120	11.01	1.15
				S 71	9.80	6.95	261	3.73	100	135	14.49	2.08
A. G.,	46	F,	1.43	C 80	11.53	9.18	199	3.57	92	80	5.84	0.64
				S 77	11.52	8.91	184	4.32	130	100	8.84	0.99
E. Z.,	48	M,	1.88	C 73	10.48	7.60	212	2.56	70	87	7.40	0.97
				S 74	12.86	9.48	222	5.16	82	95	13.39	1.41
E. P.,	43	M,	1.94	C 51	13.00	6.64	197	1.08	57	115	3.46	0.52
				S 72	12.39	8.92	239	2.18	59	130	7.87	0.88
L. S.,	39	M,	2.24	C 67	13.98	9.34	311	2.49	88	92	7.35	0.79
				S 67	13.86	9.23	290	2.17	95	127	8.35	0.90
F. N.,	60	M,	1.81	C 92	9.36	8.61	208	3.38	64	133	11.66	1.35
				S 83	9.10	7.58	217	3.17	68	148	12.15	1.60
Mean values				74	11.77	8.63	231	2.55	78	99	7.04	0.81
				72	11.82	8.51	239	3.17	91	114	9.56	1.15
p values				‡	‡	‡	‡	‡	<0.01	<0.01	<0.02	<0.01

*Control values.

†Data obtained during smoking.

‡No significant difference between control and smoking data.

the onset of smoking, which may well be qualitatively different.[6] If one assumes, however, that nicotine is the principal pharmacologic agent in tobacco smoke, then the effects of intracoronary infusion of this substance are of some interest. In the intact dog it has not been found to modify coronary blood flow when injected into the anterior descending artery, despite substantial increase in myocardial contractility.[9] Left coronary perfusion with nicotine also has failed to increase flow in the atherosclerotic rabbit heart, despite cardiac acceleration and enhanced contractility.[10] These studies, in which different methods of determining coronary flow have been employed, tend to reduce the possibility that these results in man represent an artifact of the nitrous oxide method.

Augmentation of coronary blood flow may usually be anticipated when there is an increase in heart rate, systemic arterial pressure, cardiac output, and left ventricular work. In this manner, the apparently greater oxygen requirement of the myocardium would be severed. Failure to find such increases of myocardial blood flow and oxygen consumption in the coronary subjects during cigarette smoking may plausibly be related to the "fixed coronary resistance" alleged to exist in such patients.[11] That the abnormal coronary vasculature is not responsible becomes apparent from the similar response in the subjects without evidence of coronary disease. In view of the evidence that ventricular contraction acts to impede coronary flow within the left ventricular wall,[12] the enhanced ventricular contractility as reflected by left heart work may have produced such an effect. This view is difficult to accept, since the failure of coronary flow to meet the need for greater oxygen usage should be associated with augmented oxygen extraction.

Although many of the effects of smoking and nicotine infusion mimic those of catecholamine administration,[9] an evaluation of endogenous catechols in plasma in response to smoking too small to affect the coronary vasculature appears unlikely. On the contrary, small graded doses of catecholamine induce changes in coronary flow before increments in rate and pressure.[13] Another humoral agent possibly released during smoking is antidiuretic hormone.[5] Its potent coronary vasoconstrictor properties raise the possibility that any undesirable effects of smoking could be effected through its activity. Even though the plasma levels of vasopressin probably are not sufficient significantly to restrict coronary blood flow per se, the lack of increased flow despite increments of rate and pressure may represent a restrictive effect of low hormone concentration upon the response to these stimuli of coronary vasodilatation.

It would appear that an enhanced ratio of left ventricular work to oxygen uptake may be maintained for some time without cardiac dysfunction. Such is the case in animals with chronic complete heart block[14] or in those subjected to expansion of intravascular volume.[15] Such disproportion in coronary subjects, however, if large enough, could presumably produce ischemia symptoms. This circumstance, as suggested by this study, would appear to be an uncommon occurrence.[16]

Summary

The myocardial and peripheral hemodynamic effects of cigarette smoking have been assessed during a steady state situation in a group of normal subjects, and compared with a group of patients with coronary artery disease.

During smoking, in both groups there was augmentation of heart rate, systemic arterial pressure, and left ventricular work, this response being somewhat greater in the coronary patients. Despite these hemodynamic alterations, neither group had a significant change in coronary blood flow, so that myocardial oxygen usage remained virtually identical with the value before smoking. There was no evidence of myocardial ischemia in the coronary subjects during smoking. The various factors, potentially responsible for the lack of myocardial blood flow increment are considered.

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Murmurs are not, as is often supposed, louder, *caeteris paribus,* in proportion as the valvular contraction is greater. On the contrary, the loudest murmurs are produced by a moderate contraction, and they become weak when it is extreme. A contraction of the mitral or tricuspid valve to only two, three, or four lines (one line = 1/12 inch) in diameter, I have frequently known to occasion little or no murmur.—J. HOPE. *A Treatise on the Diseases of the Heart and Great Vessels.* London, Kidd, 1832.

The Synthesis of Phospholipids in Human Atheromatous Lesions

By D. B. Zilversmit, Ph.D., Esther L. McCandless, Ph.D., Paul H. Jordan, Jr., M.D., Walter S. Henly, M.D., and R. F. Ackerman, M.D.

With the technical assistance of Anne Boals

ALTHOUGH the development of atheromatous lesions in the aorta, coronary arteries, cerebral arteries, and other large peripheral arteries of man has been correlated with a high level of serum cholesterol, cholesterol-to-phospholipid ratios, beta-lipoproteins, or Sf 10-100 lipoproteins, little direct evidence is available that the accumulation of lipids in the atheromatous aorta of man is a direct result of the deposition of abnormal blood lipids, or of normal blood lipids present in excessive amounts.

In animals a disease similar to human atherosclerosis has been produced by the feeding of high-cholesterol diets to rabbits and chicks and by more complicated regimens in rats and dogs. Even in animals no conclusive evidence is available for the origin of atheromatous lipids, although it has been shown that in the rabbit the phospholipids of the atheromatous lesions turn over quite rapidly and that at any given moment the phosphate[1] as well as the fatty acid[2] of the phospholipid molecules is derived from synthesis in situ rather than from deposition or exchange with plasma. Less evidence is available for the cholesterol present in the rabbit atheroma although the studies of Schwenk et al.[3] indicate that some of it is derived from the blood. Our own unpublished observations have also shown that the atheroma cholesterol is not synthesized in situ but participates in vigorous exchange with various cholesterol fractions of plasma.

From the Division of Physiology, University of Tennessee, Memphis, Tennessee.

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The present study was undertaken to elucidate the mechanisms whereby phospholipids accumulate in the atheromatous lesions of the abdominal aorta and of the large peripheral arteries in man.

Methods

Several types of patients were given 0.5 mc. of radioactive phosphate intravenously at various intervals prior to the removal of a portion of aorta or peripheral artery. In all experiments a blood sample was obtained at the time of surgical excision of the artery. In some experiments earlier blood samples were obtained as well. None of the patients received blood transfusions prior to removal of the artery. In cases of aortic grafting the time interval stretched from the time of injection to the time of placing the occluding clamp about the aneurysm. Excision of the aneurysm took approximately 15 minutes from the time of applying the occluding clamp. Any thrombus was immediately removed from the intima and a section of the entire wall of the aorta was obtained. From this section of the aortic wall the intima was then separated. The remaining wall including the media has been designated in this discussion as adventitia. Although the degree of fibrous reaction about the aneurysm varied from patient to patient, there was no significant variation in the thickness or gross characteristics of the intima. In one sample (no. 4, table 2) the aneurysm was comprised mainly of thrombus and intima with no adventitia present.

Sections of intima and adventitia were weighed and placed in test tubes containing methanol. Similarly 5 ml. of plasma were placed in 5 ml. of methanol. The tubes were closed with previously extracted corks, taped, and sealed with paraffin prior to shipment to Memphis. Blank tubes with methanol, but without specimen, served to check the absence of extraneous phosphorus in the final solvent mixture. The blood plasma was extracted with chloroform-methanol and purified according to the method of Folch et al.[4] Pieces of artery, intima, or adventitia were ground into small pieces, extracted for 24 hours with chloroform-methanol and purified by the same method.

Lipid extracts were analyzed for total lipid phosphorus as described previously[5] and aliquots, mounted on aluminum planchets, were counted for radioactivity with use of a lB85 Victoreen Geiger Counter.[6] Samples were in general counted in duplicate for at least 4,096 counts. When both plasma and artery samples counted less than twice background, the data were judged unreliable and rejected. Although separation of various phospholipid fractions by silicic acid chromatography was attempted, the radioactivity in the fraction was too low for reliable counting.

Results

Table 1 lists the concentrations and specific activities of phospholipids isolated from entire peripheral arteries. In 11 of 16 cases the specific activity of the arterial phospholipids exceeded that of the plasma at the end of the experiment. This is analogous to the experimental results in rabbits in which, in nearly every instance, the specific activity of phospholipids in the whole artery exceeded that of the plasma.[1] The cases in table 1 are listed in the order of their arterial phospholipid contents. As a group the peripheral arteries contained much less phospholipid than did the aortic intimas presented in table 2.

The data on phospholipid P^{32} must be interpreted with some caution, however, since many of the arteries reported in table 1 were occluded with clots or generalized atherosclerotic lesions. It is therefore possible that the low specific activities observed in some of the vessels were the result of their poor nutritional state or even a lack of viability in some cases. One can interpret the results in those cases in which the specific activity of the artery exceeded that of plasma as evidence for synthesis of the radioactive phospholipids by the vessel wall. The basis for such interpretation is the fact that radioactive isotopes migrating from one compartment to the next undergo steady dilution with nonradioactive substances with consequent decrease in specific activity. If, therefore, one assumes that plasma phospholipids are deposited within the arterial wall, one would expect to find the specific activity in the arterial phospholipids to be lower than that of the plasma. Finding the contrary situation would, therefore, be evidence against this reaction sequence and would indicate that the radioactive phospholipids were synthesized from nonlipid precursors in the artery. It might also be stated that the cases in which the specific activity of the artery was equal to, or less than, that of the plasma do not exclude the possibility that even this small amount of radioactivity was derived from synthesis. There is, then, no positive evidence in any of these experiments that radioactive phospholipids of peripheral diseased arteries are derived from the deposition of blood lipids.

Table 2 shows a summary of the data obtained on abdominal aortas and on one renal and one coronary artery. The higher content of phospholipids in the atherosclerotic aorta compared to that in the peripheral vessels is evident. Even if one allows for the fact that the femoral and popliteal arteries were analyzed whole, whereas the data in table 2 refer to split intima and adventitia, one can by recalculation of the latter data show that the average phospholipid concentration of the 15 peripheral arteries in table 1 was .253 ± .019 (SE), whereas that for the nine abdominal aortas in table 2 was .327 ± .029 mg. of phospholipid phosphorus per gram of fresh tissue. In most instances it was possible to obtain separate samples of intima and adventitia and to determine separately their respective specific activities. In eight of the 10 experiments in which P^{32} was given 12 hours or less before sampling, the specific activities of either adventitia or intima exceeded those in the plasma. In six cases the specific activity of the intima was below that of the adventitia, whereas in two instances the intima had a higher specific activity than the adventitia. In six cases the total phospholipid of the intima exceeded that of the corresponding piece of adventitia, whereas in three cases the adventitia had the greater amount of phospholipid.

It must be borne in mind that most of the arteries presented in table 2 represented abdominal aneurysms and that the metabolism

Table 1

Radioactive Phospholipids of Peripheral Arteries and Plasma after P^{32} Administration

Number	Age, sex	Tissue	Hours	Phospholipid Conc.*	S.A.†	Description
1	80, F	Plasma	8	.081	3900	Atherosclerosis; amputation of right foot, gangrene, old calcified lesions
		Popliteal		.460	1630	
2	36, M	Plasma	15.5	.0611	879	Severe atherosclerosis; occluded artery
		Popliteal		.330	1330	
3	47, M	Plasma	24	.079	2620	Gangrene, mid-thigh amputation
		Plasma	50	.077	3060	
		Femoral	50	.320	2260	
		Popliteal	50	.220	4780	
4	59, M	Plasma	8	.081	615	Atherosclerosis, fusiform aneurysm; subendothelial lipid, calcified and fibrous material; loss of elastic tissue in media
		Femoral		.315	2200	
5	71, F	Plasma	25	.063	3710	Gangrene, below knee amputation, old calcified lesions; diabetic
		Plasma	60	.062	2290	
		Popliteal	60	.314	1050	
6	69, M	Plasma	6	.037	1920	Generalized atherosclerosis; vessel completely occluded
		Femoral‡		.272	750	
		Femoral‡		.131	1220	
7	65, M	Plasma	5	.086	75	Above knee amputation, plaques
		Femoral		.235	226	
8	66, M	Plasma	11	.067	608	Atherosclerosis
		Popliteal		.225	752	
9	44, M	Plasma	6.5	.083	74	Above knee amputation
		Femoral		.223	222	
10	68, M	Plasma	6	.056	286	Atherosclerosis
		Popliteal		.212	167	
11	66, M	Plasma	6.5	.187	37	Gangrene; no intimal atherosclerosis; vessel filled with soft retrograde thrombus
		Femoral		.211	484	
12	42, M	Plasma	5.5	.090	200	Atherosclerosis
		Femoral		.198	315	
13	68, M	Plasma	12	.066	533	Severe atherosclerosis; thrombic artery, calcified lesions; diabetic
		Femoral		.194	285	
14	40, M	Plasma	6	.092	898	Rheumatoid arthritis; no intimal atherosclerosis; vessel filled with soft retrograde thrombus
		Popliteal		.181	1960	
15	75, M	Plasma	6.5	.080	664	Severe atherosclerosis; diabetic
		Femoral		.163	1540	
16	64, M	Plasma	5		409	Moderate atherosclerosis; occlusion with soft clot
		Femoral			445	

*Phospholipid concentrations expressed as milligrams of phospholipid phosphorus per gram of fresh weight.
†S.A. specific activities expressed as counts per minute per milligram of phospholipid phosphorus.
‡Intima.
§Adventitia.

of phospholipids in the wall of an aneurysm may not be the same as that of other types of atherosclerotic vessels. With this qualification, however, the evidence seems to point in the same direction as that of the peripheral vessels, namely, that active phospholipid synthesis is taking place in both the intima and the adventitia of the artery and that the radioactive phospholipid found in both places is derived by synthesis from nonlipid precursors instead of from plasma phospholipid deposition.

Table 2 presents data from one patient, a 63-year-old man, on whom necropsy was performed 66 hours after P^{32} injection. In this case it was possible to determine the phospholipid concentrations of various arteries, as well as the specific activities of the phospholipids in these arteries. Also several blood samples were taken at different time intervals after P^{32} injection. Comparison of the phospholipid content of the arteries reveals that the coronary artery and the intima of the aorta had a higher phospho-

Table 2

Radioactive Phospholipids of Aorta and Plasma after P^{32} Administration

Number	Age, sex	Tissue	Hours	Phospholipid phosphorus Total*	Conc.†	S.A.‡	Description
1	70, M	Plasma	6		.082	376	Atherosclerosis; abdominal fusiform aneurysm; marked fibroblastic proliferation and scattered deposition of lipid
		Intima		2.80	.700	257	
		Adventitia		0.758	.253	869	
2	70, M	Intima	10	3.16	.526	1360	Atherosclerosis; abdominal fusiform aneurysm; moderate thickening of intima due to intimal fibrosis and eosinophilic amorphous material containing cholesterol clefts
		Adventitia		1.54	.154	700	
3	61, M	Plasma	9.5		.087	484	Abdominal aneurysm; fibrosis of media, marked subendothelial lipid and calcified material; inflammatory reaction in adventitia
		Intima		.418	.523	183	
		Adventitia		.281	.141	238	
4	67, M	Plasma	8		.084	832	Atherosclerosis; large abdominal fusiform aneurysm; thin fibrous wall infiltrated by numerous lymphocytes and plasma cells
		Intima		1.210	.402	954	
		Thrombus		1.380	.231	98	
5	58, M	Plasma	9		.085	174	Atherosclerosis; abdominal aneurysm; thick fibrous wall with lymphocytes and plasma cells; thickened intima partially hyalinized and calcified
		Intima		.795	.390	240	
		Adventitia		.681	.244	1490	
6	71, M	Plasma	9		.080	319	Atherosclerosis; abdominal aneurysm; thin portion of artery showing extensive fibrosis, lipid, and calcium in the region of the inner surface
		Intima		.351	.351	469	
		Adventitia		.288	.240	134	
7	51, M	Plasma	7.5		.136	101	Abdominal aneurysm; occlusive vascular disease of lower extremities; intima and media completely replaced by cholesterol clefts and organizing thrombus
		Intima		.278	.348	52	
		Adventitia		.328	.273	140	
8	56, M	Plasma	12		.076	656	Atherosclerosis; abdominal fusiform aneurysm; marked fibrosis with hyalinization with few remaining cellular elements
		Intima		1.883	.314	688	
		Adventitia		1.76	.314	1575	
9	62, F	Plasma	12		.078	1015	Atherosclerosis; renal artery, old calcified lesions
		Renal artery			.309	1560	
10	63, M	Plasma	8.5		.104	69	Atherosclerosis; abdominal aneurysm; marked fibrosis in the wall with intimal lipid
		Intima		1.034	.188	37	
		Adventitia		1.427	.476	263	
11	60, M	Plasma	17		.065	2150	Abdominal aorta, necropsy
		Artery			4.52§	450	
12	63, M	Plasma	17		.080	1975	Cerebral infarction due to atherosclerosis, old calcified and yellow lesions
		Plasma	29		.079	3170	
		Plasma	42		.082	3760	
		Adventitia	66		.350	959	
		Superficial Intima	66		.480	1505	
		Deep intima	66		.610	590	
		Coronary	66		.540	840	
		Liver	66		.810	5070	

*Phospholipid total refers to lipid phosphorus in the intima and corresponding adventitia samples.
†Phospholipid concentration expressed as milligrams of phospholipid phosphorus per gram of fresh weight.
‡S.A. specific activities expressed as counts per minute per milligram of phospholipid phosphorus.
§Expressed on dry weight basis.

lipid content than the aortic adventitia. The specific activity of the superficial intima was higher than that of the adventitia, whereas the deeper intima had a lower specific activity. The coronary artery showed an intermediate phospholipid specific activity. The liver, of course, showed a high rate of incorporation of P^{32} into its phospholipid fractions.

Although this case does not provide any evidence with regard to the origin of the phospholipids in the various tissues, it does at least allow some comparison of a piece of coronary artery with different portions of aorta from the same patient.

Discussion

As shown above, upon injection of P^{32} in patients with vascular disease, it is possible to recover considerable quantities of radioactive phospholipids in the intima and adventitia of the abdominal aorta as well as in peripheral vessels with atherosclerotic lesions. In several instances the specific activity of the phospholipids in the artery exceeded greatly the specific activity in plasma. This was particularly true at the early time intervals after P^{32} injection when the plasma had not yet reached its maximum specific activity. It would therefore appear important in further experiments to obtain specimens of artery soon after isotope administration.

In order for a difference of specific activity between artery and plasma to signify that phospholipids are synthesized locally rather than derived from deposition of blood phospholipids, one should have evidence that the lipid fractions are relatively homogeneous. Chemical analyses of human and rabbit atheromatous lesions have revealed, however, that many different phospholipids are present. It is, therefore, not strictly valid to compare the specific activities of phospholipid mixtures in the arterial wall with those of plasma. If one may draw a comparison between the situation in man and that found in the cholesterol-fed rabbit, however, it may be pointed out that the differences in specific activity between whole phospholipid fractions in artery and plasma were not greatly modified by separating each fraction into individual phospholipid components.[7] It is therefore likely that, if one had enough radioactive material to perform such an experiment in man, one would find that the specific activity differences of the individual phospholipid fractions do parallel the difference of the whole phospholipid fraction.

In the cholesterol-fed rabbit one can, by removal of the liver, intestinal tract, and kidneys, severely depress the formation of radioactive phospholipids. Under these conditions the incorporation of P^{32} into the intimal lesions was independent of such a suppression.[5] This, of course, strengthens the evidence that the metabolism of phospholipids in the aorta is relatively independent of that in the plasma, and that, in the rabbit, the aortic phospholipids are almost entirely of local synthetic origin. Much more refined experiments are necessary in order to draw similar conclusions in patients.

Further evidence that the nonsterol lipid in atheromatous lesions of man is derived from metabolic processes in situ is provided by the studies of Geer et al.[8] These investigators found that, with the exception of some extracellular cholesterol crystals, the lipid that appeared in fatty streaks and fibrous plaques was intracellular, and was especially prominent in smooth muscle cells of human coronary and aortic arteries. Moreover, Böttcher et al.[9] found less oleic and linoleic acid in the phospholipids of atherosclerotic aortas than in plasma phospholipids. This finding might, of course, represent a selective uptake of plasma phospholipids by the aorta but it more likely represents de novo synthesis of phospholipids by the artery. The conclusion is therefore suggested that in man, as well as in the rabbit, the phospholipids of the artery have a metabolism of their own and are not merely static deposits of plasma phospholipids or plasma lipoproteins.

Summary

Femoral arteries, abdominal aortas, one renal artery, and one coronary artery removed from patients injected with P^{32} phosphate showed in most instances an active incorporation of the label into the phospholipids of intima and adventitia. A comparison of the specific activities of arterial plaque and plasma phospholipids suggests that the excess arterial phospholipids are originally derived from synthesis by the arterial wall, or at least undergo continuous renewal in situ.

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The Teacher

I envy no man that knows more than my self, but pity them that know less. I instruct no man as an exercise of my knowledge, or with an intent rather to nourish and keep it alive in mine own head then beget and propagate it in his: and in the midst of all my endeavours there is but one thought that dejects me, that my acquired parts must perish with my self, nor can be Legacied among my honoured Friends.—Sir Thomas Browne. *Religio Medici.* Edited by W. A. Greenhill, M.D. London, Macmillan and Co., Ltd., 1950, p. 97

Studies on Digitalis

III. The Influence of Triiodothyronine on Digitalis Requirements

By Robert L. Frye, M.D., and Eugene Braunwald, M.D.

THERE HAS BEEN considerable interest in whether or not changes in the thyroid state modify the effectiveness of digitalis. A number of reports have suggested that patients with hyperthyroidism associated with congestive heart failure or atrial fibrillation are relatively unresponsive to the usual doses of digitalis.[1–8] Others have indicated, however, that these patients may respond to the ordinary dose of digitalis.[9–11] Some observers[5] have advocated that great caution should be exercised in administering digitalis to patients with thyrotoxicosis, and the possibility that digitalis may result in myocardial necrosis in hyperthyroidism has been suggested by experimental studies.[12]

These widely varied views are based primarily on clinical impressions. The present investigation was therefore designed to evaluate, in quantitative fashion, the changes in digitalis requirements that follow alteration of the thyroid state induced by triiodothyronine administration. In addition, an attempt was made to elucidate the mechanism involved in the observed changes in digitalis requirements. Portions of this study have been presented elsewhere in preliminary form.[13]

Methods

Six patients with inactive rheumatic heart disease and one patient (F.G.) with arteriosclerotic heart disease were studied; these patients ranged in age from 20 to 60 years and all had chronic atrial fibrillation. None of the patients was in congestive heart failure at any time during the investigation. One patient (J.D.) had been rendered myxedematous by means of I^{131}-induced thyroid ablation for congestive heart failure, which had existed 2 years prior to this study. One patient had spontaneous myxedema.

Alterations of the metabolic state were induced by the daily oral administration of 75 to 500 μg. of triiodothyronine (T^3) in divided doses, or by a single intravenous injection of this drug. The effects of this medication on heart rate, basal metabolic rate, serum cholesterol, and protein-bound iodine were noted. In all patients in whom hyperthyroidism was induced by means of oral T^3, an increase in nervousness, fatigability, and sweating was observed. The ventricular rate was utilized to provide a quantitative expression of digitalis effect throughout these studies. In all but the first patient described below, the resting ventricular rates were determined each morning for a 2-minute period after the patient had been in the recumbent position for 30 minutes.

From the Section of Cardiology, Clinic of Surgery, National Heart Institute, Bethesda, Maryland.

Experimental Procedures and Results

I. J.D., a myxedematous patient with rheumatic heart disease and chronic atrial fibrillation, was studied by determining the manner in which the administration of T^3 altered the amount of acetylstrophanthidin required to achieve a given reduction in ventricular rate. The individual determinations of acetylstrophanthidin requirement were performed in a constant manner. On arrival in the laboratory the patient remained at complete rest in bed for 15 minutes, during the last 10 minutes of which the control ventricular rate was recorded. In this particular patient attempts were made to minimize the vagal effects of digitalis and to provide a comparable starting ventricular rate at various levels of T^3 dosage. This was accomplished by atropine sulfate, which was administered intravenously in a dose ranging from 0.50 mg. to 1.0 mg. When the patient was myxedematous and the control ventricular rate was low, the dose of atropine was 1.0 mg. After the administration of T^3, however, as the patient became euthyroid, the dose was lowered to 0.50 mg. Immediately following this injection, a continuous infusion of 0.018 mg. per minute of atropine sulfate was begun and was maintained by means of a Bowman infusion pump through-

out the remainder of each study. This procedure made it possible for the ventricular rates to be in a comparable range (av. = 92 beats per minute) at the onset of each acetylstrophanthidin infusion. Thirty minutes following the initial injection of atropine, an acetylstrophanthidin infusion was begun at a rate of .03 mg. per minute by means of a second Bowman infusion pump, and the ventricular rate was recorded electrocardiographically during every alternate minute. The amount of acetylstrophanthidin required to reduce the ventricular rate to 70 per minute and the amount necessary to result in an absolute reduction in the ventricular rate of 20 beats per minute were determined.

Figure 1 illustrates the response of the patient to the infusion of acetylstrophanthidin when he was myxedematous, and also after he had been rendered euthyroid with 75 μg. of T^3 daily. It is evident that in order to produce a comparable decrease in ventricular rate, the acetylstrophanthidin had to be infused for only 16 minutes, a total of 0.48 mg., when the patient was myxedematous, whereas a 50-minute infusion, i.e., a dose of 1.50 mg., was required when he was euthyroid.

The results of the entire study are presented in figure 2. When the patient was hypothyroid, the amount of acetylstrophanthidin required to reduce the ventricular rate to 70 per minute ranged from 0.48 to 0.72 and averaged 0.58 mg. At this time 0.48 mg. to 0.72 mg. (av. = 0.54 mg.) of acetylstrophanthidin was required to reduce the ventricular rate by 20 beats per minute from the rate existing at the time the infusion was begun. After the patient had been rendered euthyroid by the administration of 75 μg. per day of T^3, the serum cholesterol fell and the control ventricular rate rose. The acetylstrophanthidin required to reduce the ventricular rate to 70 per minute increased to 1.50 mg. and the amount necessary to result in an absolute reduction in ventricular rate of 20 beats per minute increased to 0.84 mg. Three to 4 weeks after the T^3 had been discontinued the acetylstrophanthidin requirement fell to the levels that were observed prior to the T^3 administration, and the cholesterol and control ventricular rates returned to their previous levels.

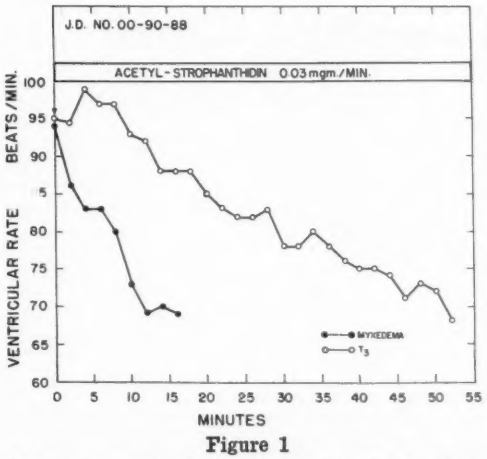

Figure 1

Ventricular rate during constant acetylstrophanthidin infusion. The closed circles represent observations carried out when the patient was myxedematous. The open circles represent observations made when the euthyroid state had been achieved by oral T^3 administration. The acetylstrophanthidin was discontinued at 16 and 50 minutes, respectively, in the two studies.

II. One myxedematous and three euthyroid patients were studied by determining the resting ventricular rates each morning while they were on a constant maintenance dose of oral digoxin. T^3 was then administered at a constant dose to each patient, this dose ranging from 100 to 250 μg. per day. After the T^3 effect had stabilized, and while the drug was continued, the additional amount of oral digoxin required to reduce the ventricular rate to control levels and to maintain it at these levels was determined. Both in patients C.C. (fig. 3) and S.C. the dose of digoxin during the control period was 0.20 mg. and in order to return the ventricular rate to control levels during the T^3 administration, the daily dose of digoxin had to be increased to 0.90 mg. In patient C.C. (fig. 3) the dose had to be maintained at this elevated level in order to maintain the ventricular rate at control levels. In patient W.P. a total of 2.30 mg. of digoxin, administered over a 2-day period, was necessary to return the ventricular rate to control

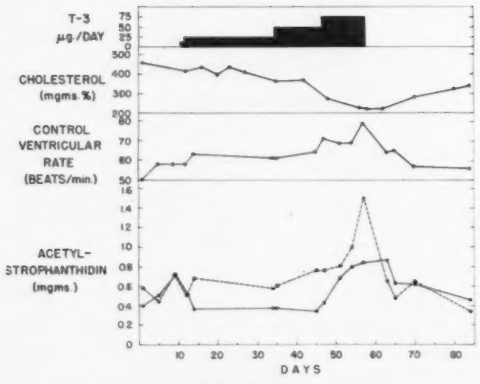

Figure 2

Observations on acetylstrophanthidin requirements before, during, and after T^3 administration in patient J.D. In the lowest panel, the points joined by the broken line represent the dose of acetylstrophanthidin required to reduce the ventricular rate to 70 beats per minute, while the points joined by the solid line represent the dose required to reduce the ventricular rate by 20 beats per minute from the rate existing at the time the infusion was begun. The control ventricular rate represents the basal rate prior to the atropine administration.

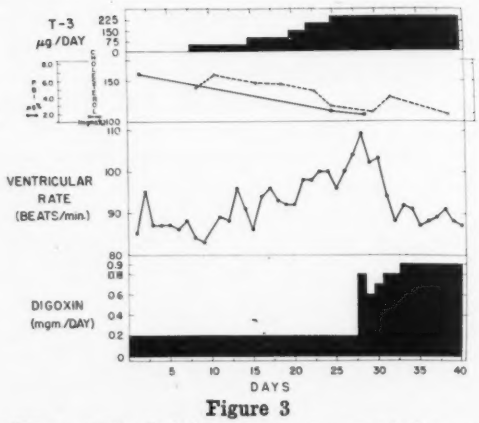

Figure 3

Effect of T^3 administration on the ventricular rate and on the dose of digoxin required to return it to the control level in a euthyroid patient.

levels, and a daily dose of 0.80 mg. per day was required to maintain the ventricular rate at control levels. When the daily dose was lowered to 0.40 mg. per day, the ventricular rate rose again. In all three patients, the relatively large doses of digoxin that were administered were tolerated without evidence of toxicity.

In the myxedematous patient (C.E.) the increased ventricular rate during T^3 administration was reduced only slightly by increasing the daily oral dose of digoxin from 0.25 mg. to daily doses ranging between 0.65 and 1.37 mg. and averaging 1.05 mg. The total dose of digoxin required to return the resting ventricular rate to the control level could not be assessed, since this patient developed gastrointestinal manifestations of digitalis intoxication.

III. Three euthyroid patients were studied by determining their morning ventricular rates first while they were on a constant dose of oral digoxin and then after they had also been given T^3. Reserpine or syrosingopine was then administered intramuscularly and the changes in ventricular rate were noted while the same doses of digoxin and T^3 were continued. In all three patients the ventricular rate returned to the levels that existed before the administration of T^3 without additional digoxin (fig. 4).

IV. Two euthyroid patients who were maintained on a constant daily dose of digoxin were studied by noting the change in the daily ventricular rate after an intravenous injection of T^3. These observations were made both before and after the administration of syrosingopine. In one patient (F.G., fig. 5) the increase in ventricular rate resulting from T^3 was almost completely prevented by syrosingopine, while in the other patient (C.C.) it was partly prevented.

Discussion

These results indicate that T^3 increases the digitalis requirements in patients with chronic atrial fibrillation and thus they are in agreement with those observations suggesting that hyperthyroid patients with atrial fibrillation do not respond in a normal fashion to the usual doses of digitalis.[1, 2, 4] The present study permitted a quantitative estimation of the alterations in digitalis requirement associated with variations in the thyroid state. The induction of mild thyrotoxicosis in patients with chronic atrial fibrillation resulted in a

three- to four-fold increase in the dose of digoxin required to maintain the ventricular rate at the level that was present in the euthyroid state. Similarly, the induction of a euthyroid state in previously hypothyroid patients also resulted in an increase in digitalis requirements. These augmented digitalis requirements resulted not only from an increase in the resting ventricular rate, but also from the larger doses needed to achieve any given amount of slowing of the ventricular rate during T^3 administration (figs. 1 and 2).

Throughout this study the slowing of the ventricular rate in patients with atrial fibrillation was utilized to provide a clinical index of digitalis effect. This procedure is similar to that employed by Gold and his collaborators for comparing the onset and duration of action of various glycosides.[14-16] In patients with atrial fibrillation the ventricular rate is largely determined by the refractory period of the atrioventricular node,[17] and the action of digitalis glycosides in prolonging this refractory period is well established.[17] Woodbury and Hecht, however, in studies with single heart muscle fibers, have demonstrated a dissociation of electrical and mechanical effects of glycosides.[18] Hemodynamic studies have also suggested that in patients with atrial fibrillation the positive inotropic action of the glycosides is not necessarily reflected precisely by the slowing of the ventricular rate.[19, 20]

It was evident that when large doses of digitalis were administered the tachycardia resulting from T^3 administration could be abolished, and it was of interest that manifestations of digitalis intoxication occurred in only one of the patients who was given these large amounts of the drug. Thus, the observations presented herein are not consonant with the view that digitalis is of little value in controlling the ventricular rate of hyperthyroid patients with atrial fibrillation.[21, 22] Although it has been suggested that digitalis should be administered with great caution to patients with thyrotoxicosis, it is difficult to determine the susceptibility of these patients to digitalis intoxication. In addition to atrial

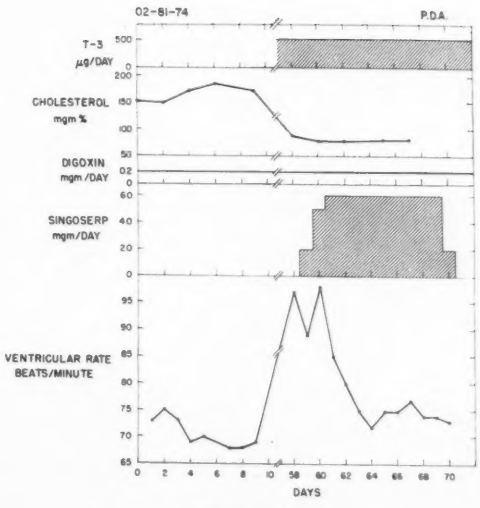

Figure 4

Effect of T^3 on the ventricular rate of a patient on a constant dose of digoxin, and the reversal of this effect by syrosingopine. The graph is interrupted from the tenth to the eighty-fifth day of the study, during which the T^3 dosage was gradually increased until clinical evidence of hyperthyroidism was evident.

fibrillation, a variety of arrhythmias, including premature beats,[23] heart block,[24] and ventricular tachycardia,[25] have been described in undigitalized hyperthyroid patients, thus making it difficult to evaluate the role of digitalis in producing such disturbances in rhythm and conduction. Although the possibility that digitalis administration is hazardous in the presence of hyperthyroidism was suggested by a study in which this drug was reported to produce areas of myocardial degeneration in hyperthyroid cats,[12] these results cannot be readily transferred to man.

The mechanism of the observed increase in digitalis requirements with T^3 administration is not clear. It is certainly possible that changes in the thyroid state modify the metabolism or inactivation of digitalis. It was evident, however, that both reserpine and syrosingopine abolished these increased digitalis requirements (figs. 4 and 5). It is now well established that these rauwolfia alkaloids deplete a variety of tissues of their stores of

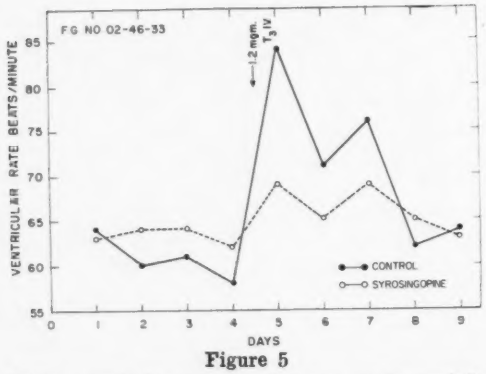

Figure 5

Daily ventricular rates during two study periods of 9 days each. On the fourth day of each period, 1.2 mg. T^3 was injected intravenously. The solid points represent observations made while the patient was receiving 0.15 mg. of digoxin daily. The open circles represent observations made while the patient received the same daily dose of digoxin, but in addition, 4.0 mg. of syrosingopine daily for 4 days before and 3.5 mg. daily for 5 days after the injection of T^3.

norepinephrine.[26-30] However, syrosingopine is only one tenth as active as reserpine in depleting the brain of amines, although it is as effective in depleting the heart's stores of norepinephrine.[31] This difference in action of the two drugs is thought to be the basis for the significant sedative and depressive effects noted with reserpine and the absence of these effects with syrosingopine. Thus, it may be postulated that the abolition by reserpine or syrosingopine of the T^3-induced augmentation of digitalis requirements is related to the depletion of norepinephrine from the heart and is independent of any sedative effects. This hypothesis receives support from the experiments of Brewster et al.,[32] who demonstrated in dogs that total sympathetic blockade prevented the metabolic and hemodynamic effects of thyroid feeding. Both reserpine and syrosingopine, however, also possess parasympathomimetic actions,[33] which could also have been responsible for the prevention of the T^3-induced augmentation of digitalis requirements.

In spite of a lack of complete understanding of its mechanism of action, reserpine has been administered to patients with thyrotoxicosis and has resulted in an amelioration of the signs and symptoms, including the hypermetabolism and tachycardia.[34, 35] Reserpine has also recently been demonstrated to have a bradycrotic effect in euthyroid patients with atrial fibrillation.[36] Thus, in the clinical management of hyperthyroid patients with atrial fibrillation and a rapid ventricular rate, it would seem appropriate to utilize both digitalis and syrosingopine. The latter drug would be useful in decreasing the digitalis requirements in such patients and should thus eliminate the need for large doses of digitalis. The syrosingopine should be administered intramuscularly in order to obtain the prompt effects that are desired in such a clinical situation, since after the initiation of oral therapy the bradycrotic effects are not apparent for several days.[36] It must, however, be emphasized that syrosingopine or reserpine does not eliminate the need for specific antithyroid therapy.

Summary

The effects of triiodothyronine (T^3) administration on digitalis requirements was studied in a group of patients with atrial fibrillation. The ventricular rate was utilized to provide a quantitative expression of digitalis effect. In one patient the amount of acetylstrophanthidin, administered as a constant infusion, required to slow the ventricular rate to 70 beats per minute rose from an average of 0.58 mg. while he was myxedematous, to 1.50 mg. when he was euthyroid. When mild thyrotoxicosis was induced in three euthyroid patients the daily dose of digoxin had to be increased approximately four-fold in order to maintain the ventricular rate at a control level. In three patients it was observed that reserpine or syrosingopine administered intramuscularly abolished the increased requirements for digoxin induced by T^3. In two patients syrosingopine was found to prevent partially the tachycardia resulting from large doses of intravenous T^3. The possible mechanisms responsible for these effects and their therapeutic implications are discussed.

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Quite as interesting as the advance in our control of disease, and perhaps as significant for the future, our interpretation of disease, and consequently our ways of reacting to it, have changed. In the past more than once they have changed, and usually in the direction of a less superstitious and more rational attitude. As the concept of disease has become more rational, it has involved, in one form or another, the recognition of how wise it is for the individual to be concerned with the health of others, as an aid to his own safety. Scientific knowledge of communicable disease demonstrated beyond any question the social aspects of individual illness, and the importance to one and all of a healthy common environment.—Alan Gregg, M.D. *Challenges to Contemporary Medicine.* New York, Columbia University Press, 1956, p. 80.

Premature Ventricular Depolarization

By CESAR A. CACERES, M.D.

A DIFFERENCE has been observed in certain instances between the onset of QRS in intracavitary and surface limb leads. Simultaneous tracings demonstrate that when premature ventricular depolarization exists the early rapid growth in magnitude of potential recorded by intracavitary leads may be nearly or totally inapparent in surface leads. Following premature depolarization changes occur in intracavitary and surface leads that shed light on the electrical basis for surface electrocardiographic inscription of "fusion beats," initial and terminal QRS abnormalities, and secondary ST-T wave changes.

Materials and Methods

Premature ventricular complexes were observed during the course of 50 consecutive right- and left-sided heart catheterizations performed separately or as combined procedures. The intracavitary electrocardiogram was recorded simultaneously with surface leads and usually with cavity pressure curves. A multichannel cathode-ray tube recorder* with a photographic recording system and a paper speed of 75 mm. per second was used to record tracings of simultaneous conventional electrocardiographic leads, unipolar intracavitary leads, and intracavitary pressures. Time lines in the records are separated by 0.02 second. Amplifier sensitivity was usually 30 mm. per millivolt. High-frequency amplifier cut-off in the illustrations conforms to that of direct-writing electrocardiographs. Cardiac pressures were recorded with strain gages.† Esophageal leads were recorded as unipolar leads with an esophageal electrode catheter.‡

Each electrocardiographic lead was recorded by separate sets of electrodes and separate but matched amplifiers. The surface lead generally selected for comparison with the intracavitary lead was the one most parallel to the QRS axis for the subject, since that was found to have a better signal-to-noise ratio than others. Two conventional surface leads were used to demonstrate that absence of changes in an isolated surface lead were not due to perpendicularity of an electrical current to the plane of that lead. Electrode catheters were used to record intracavitary electrocardiograms. Right intracavitary leads were recorded with Cournand electrode catheters* connected to exploring electrodes of Wilson central terminals. Left intracavitary leads were obtained by means of a thin copper wire inserted through the polyethylene catheter utilized in percutaneous transthoracic catheterization of the left heart. The tip of the wire was at the distal end of the catheters and its proximal portion was connected to the exploring electrode of a Wilson central terminal. The intrinsic deflection of the intracavitary lead was used as a measure of time of occurrence of depolarization in the region of the electrode catheters.

Comment

This paper deals predominantly with right ventricular complexes because of the greater number of right cardiac catheterizations performed in our laboratory. Study of the more limited left heart catheterization material suggests that findings from the left will be qualitatively the same as from the right. During cardiac catheterization premature beats are frequently induced. All of the complexes in this study could be considered to be due to the presence of the catheter within the heart. We assume that premature complexes in the presence or absence of a cardiac catheter follow similar patterns and electrical principles. All the subjects in this study had acquired or congenital heart disease and were included in this study without regard to age, sex, or diagnosis. Tracings were selected to illustrate findings common to the group of patients catheterized.

Results

Figure 1

"Normal sinus rhythm" is present throughout the tracing. The third ventricular complex is

From the Department of Medicine, The George Washington University Hospital, Washington. D. C.

*Electronics for Medicine, White Plains, New York.

†Statham Instruments Inc., Los Angeles, California.

‡Sanborn Company, Waltham, Massachusetts.

*U. S. Catheter Company, Glens Falls, New York.

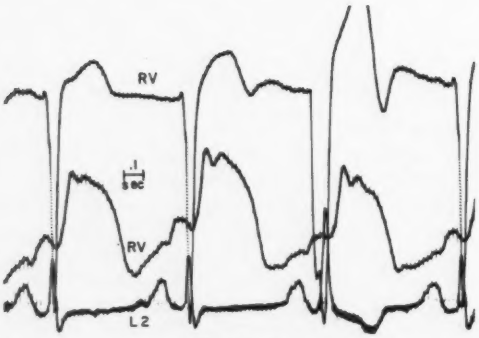

Figure 1

Simultaneous right ventricular intracavitary electrocardiogram (top) right ventricular intracavitary pressure curve (middle) and lead II electrocardiogram (bottom). Time scale in figure 1 applies to all figures except figure 4. The 30-mm. per millivolt scale in figure 3 is applicable to all surface leads except in figure 4. The intracavitary complexes were recorded at either 5 or 30 mm. per millivolt. The intracavitary leads in figure 3, and the left ventricular leads in 5B and 8 were recorded at the former sensitivity to allow full visualization on the figures.

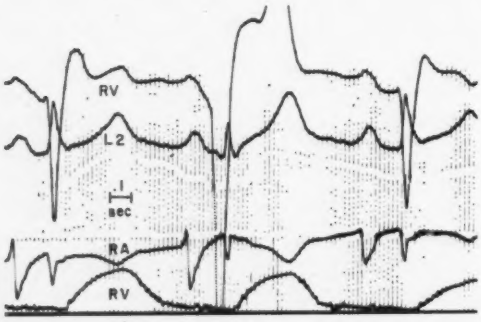

Figure 2

See legend for figure 1.

abnormal, due to premature right ventricular depolarization manifested by the early intrinsic deflection of the right ventricular lead. Evidence of premature ventricular depolarization at its actual time of occurrence is lacking in lead II. Shortening of "P-R segment," increase of QRS amplitude, disappearance of S wave, and secondary ST-T-wave changes are seen after the premature right ventricular depolarization.

A notch is present near the bottom of the descending limb of the intracavitary QRS in the abnormal complex. This notch is present at the onset of the normal intracavitary complexes. The

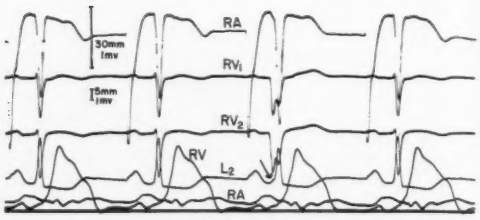

Figure 3

See legend for figure 1.

time intervals between these notches in all complexes are the same as the P-P intervals and the intervals between intracardiac pressure points.

Conclusions

It is likely that the notch and the subsequent portion of the intracavitary lead is due to the sequence of normal activation in the right ventricle. In the third beat premature ventricular depolarization is apparently aborted by normal processes. The area of myocardium responsible for the S wave may have been the source of the premature depolarization. Although the usual order of electrical events in the right ventricle is disturbed, there is no visible change in the pattern or rhythmicity of the right ventricular pressure curve.

Figure 2

In the second cardiac cycle premature depolarization is evident in the right ventricular lead, but simultaneous changes suggestive of early depolarization are not seen in the limb or atrial leads. Two hundredths of a second after the intrinsic deflection in the intracavitary lead the QRS complex of lead II shows an 0.04 second Q wave, decreased QRS amplitude, a slightly prolonged Q-T interval, S-T elevation, and secondary T-wave changes. The right atrial lead does not disclose significant simultaneous potential changes. In contrast to figure 1, in which the rhythmicity of ventricular pressure pulses was unchanged, prematurity of right ventricular depolarization was accompanied by a 0.02-second earlier onset of rise of ventricular pressure.

Conclusions

Premature onset of the ventricular pressure may or may not accompany premature ventricular depolarization. Premature right ventricular depolarization can produce isolated complexes in which QRS contours and secondary ST-T-wave changes in the limb leads are similar to patterns associated with myocardial infarction.

Figure 3

Normal sinus rhythm is present throughout the tracing. The third beat shows premature right

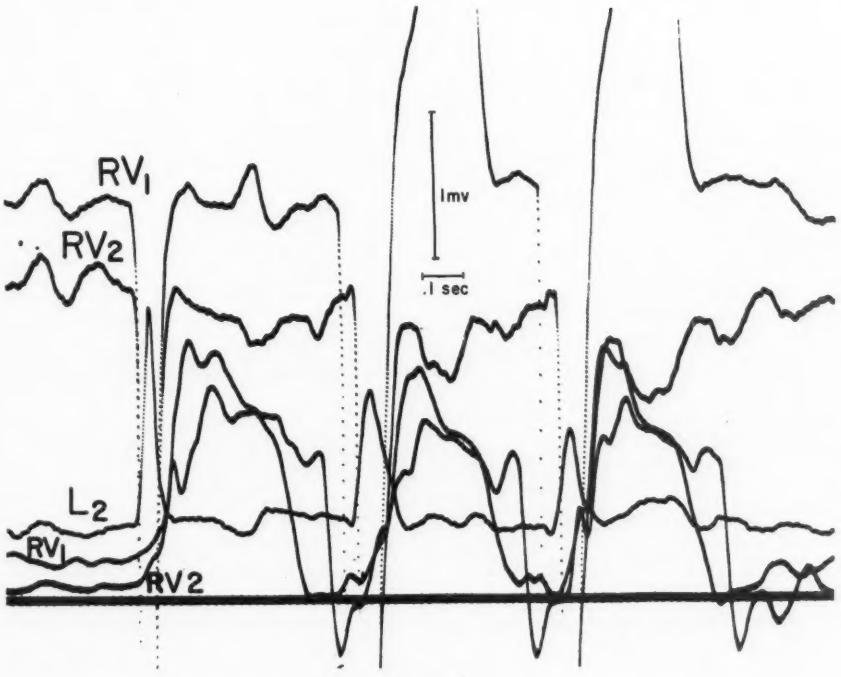

Figure 4

See legend for figure 1.

ventricular depolarization of about 0.03 second in both ventricular leads taken with separate electrodes 1 mm. apart on the same catheter. Lead II demonstrates a short P-R interval and a small positive upstroke before the usual R wave. The right atrial lead shows a minor change in the downstroke of its QRS but no clear evidence of right ventricular prematurity. In the right ventricular pressure curve, the third beat is approximately 0.02 second shorter than the others. Only the descending limb of the right ventricular pressure curve shows minimal alteration in its contour.

Conclusions

Early depolarization of a portion of myocardium may not materially affect the basic pattern of other intracavitary deflections, and surface electrocardiographic changes may be minimal. In this tracing the QRS deflection in the right atrial lead showed no significant change due to the right ventricular depolarization, suggesting that the abnormality was generated by a small myocardial area. This may be the reason why only minimal changes in duration and contour of pressure waves accompany premature ventricular depolarization. In this tracing terminal forces of depolarization seen in the normal beats have apparently shifted to the initial portion of the abnormal cycle without disturbing the depolarization of the myocardial areas responsible for major QRS and ventricular pressure curves.

Figure 4

The first sequence is the normal one for this subject with atrial fibrillation. Electrode catheter RV_1 was at the tricuspid valve level and RV_2 was at the pulmonic valve level. The second and third sequences showed markedly asynchronous depolarization within the same ventricle. Depolarization occurred prematurely 0.04 second earlier at the tricuspid valve level than at pulmonic valve. Lead II showed a small Q wave, a prolonged QRS of lower than normal voltage, and ST-T-wave changes. Pressure pulse contours are normally different at each valve level (1st complex). The duration of ventricular systole decreased after the asynchronous depolarization (second and third complexes).

Conclusions

Within the same ventricle there are areas of myocardium more susceptible than others to premature depolarization; conversely premature depolarization represents a segmental or localized change in pattern of depolarization. The shortened

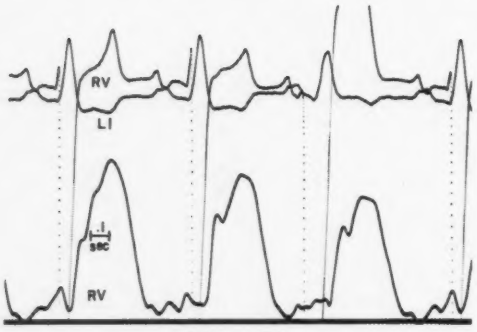

Figure 5A

See legend for figure 1.

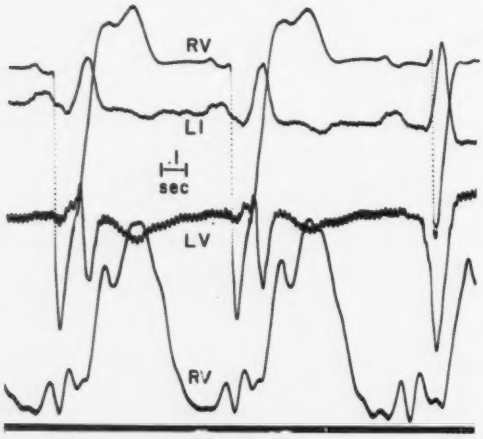

Figure 5B

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ventricular systole may be due to premature depolarization but could also be a manifestation of changes in R-R interval.

Figures 5A and 5B

In the third cycle of 5A right ventricular depolarization is 0.09 second premature and right ventricular pressure is 0.03 second early. Lead I shows no changes directly simultaneous with the early inscription of the intrinsic deflection. Immediately following premature ventricular depolarization lead I shows a decreased P-R interval, a Q wave of 0.03 second duration, decreased QRS amplitude, and Q-T prolongation.

Figure 5B from the same subject shows the same situation in the first two cardiac cycles. A simultaneous left ventricular lead has also been recorded. Approximately a 0.1-second difference exists between the onset of the intrinsic deflection in the right and left ventricular complexes during the time that the surface lead records the Q wave.

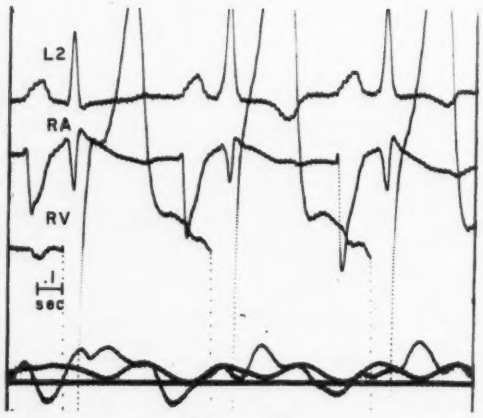

Figure 6A

See legend for figure 1.

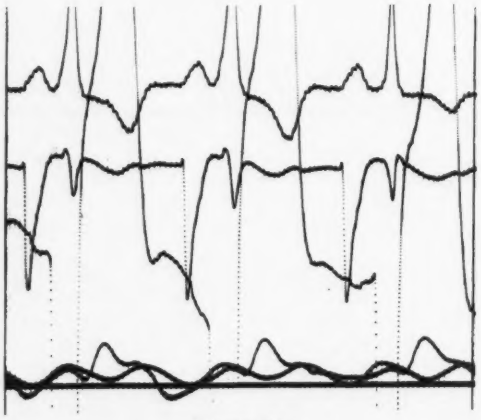

Figure 6B

See legend for figure 1.

In the normal third complex there is no longer a marked "phase" difference between the intrinsic deflection of right and left ventricles. The period for the intrinsic deflections of the left ventricle is constant for all cycles as is the P-P interval. The period for the intrinsic deflection of the right ventricle is not constant because of premature right ventricular depolarizations.

Conclusions

Since atrial and left ventricular complexes are regular throughout the tracing, the abnormal surface complexes may be assumed to be due to right ventricular premature depolarization. A series of beats, as well as isolated ones (fig. 3) with changes like those associated with myocardial infarction can occur with premature right ventricular depolarization. The marked electrical

asynchronism between left and right ventricles was the apparent cause of the surface lead changes.

Figures 6A and 6B

The periods between the intrinsic deflection of all right atrial P waves and right atrial QRS complexes are identical and constant in these two continuous tracings. The P waves in lead II do not change in contour or timing. Since the intrinsic deflection of the atrial P wave is constant, the intrinsic deflection of the right ventricular lead can be referred to it for timing purposes. The intrinsic deflection of the right ventricle does not maintain a constant period. In the first cycle a small Q wave and a small S wave are present in lead II along with an isoelectric T wave. In subsequent cycles the Q and S waves are no longer present, the "P-R segment" is of varying duration, the QRS duration increases slightly, the QRS amplitude becomes greater, and secondary ST-T-wave changes occur.

Conclusions

The degree of shortening of "P-R segment," QRS abnormalities, and secondary ST-T-wave changes in the limb lead reflect the degree of prematurity of ventricular depolarization. As the interval between atrial and ventricular depolarization shortens (measured here from intrinsic deflection of the atrial P wave to that of the right ventricular QRS) these changes become more pronounced. In an individual subject similar surface electrocardiographic complexes tend to have the same atrial ventricular depolarization time. (Examples: Sequences 3 in figure 6A and 3 in 6B, sequences 1 and 2 in 6B). The decreasing P-R interval with increasing changes in QRS suggests the "concertina effect" in the Wolff-Parkinson-White syndrome.

Figure 7

The second sequence shows premature right ventricular depolarization following premature atrial activity. A shift toward right axis deviation is present. Lead I has a Q wave of 0.03 second duration, decreased QRS amplitude, and minor T-wave changes. Lead III has greater amplitude of QRS and T. Right ventricular QRS and T amplitude greatly increased after premature activation of right ventricle. Right ventricular pressure was also early and had during the abnormal sequence a decrease in systolic pressure and alteration of its configuration. The phonocardiogram preceding the instance of prematurity demonstrated splitting of the second sound.

Conclusions

Prematurity of ventricular activation causes shifts of electrical axis as seen in surface leads. The large ventricular amplitude found during premature activation is not proportionally displayed on the surface although it is suggested by changes in the electrical axis of the forces of the premature depolarization. The large electrical potential of premature depolarization is not associated with an increment of ventricular pressure but rather with a decrease and a change in the pressure curve.

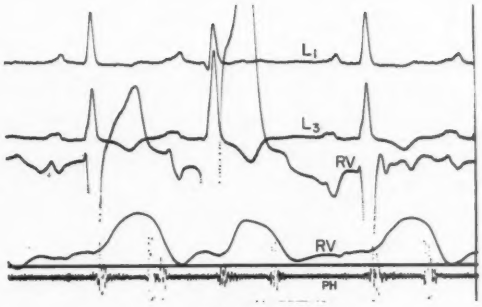

Figure 7

See legend for figure 1.

Figure 8

The first and fourth complexes are normal for the subject. The third complex is an interpolated premature ventricular contraction. The tracing shows simultaneous right and left ventricular leads (left ventricle was recorded at one-sixth the sensitivity of the other leads) left atrial, and lead II. The P waves in the left atrial curve show "normal sinus rhythm" throughout. The second complex demonstrates approximately 0.04 second early depolarization of left ventricle. The amplitude of the left ventricular QRS increased about twice and QRS area about four times during the instance of prematurity, but the right ventricular complex shows no change, and early left ventricular depolarization was evident in right ventricle by ST-T-wave changes only. The left atrial QRS showed a Q wave approximately three times deeper than found during the normal beats. Left atrium and lead II have a shorter than normal P-R interval. The QRS is slightly increased in amplitude in lead II and the ST-T-wave area is more depressed than in normal beats.

Conclusions

Left ventricular premature depolarization produces surface and intracavitary changes similar to changes seen during premature right ventricular depolarization.

Discussion

It is suggested by these studies that the initial electrical forces of premature ventricular complexes begin before they are apparent on conventional surface leads. In instances

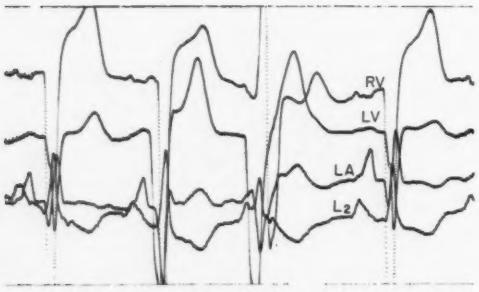

Figure 8

See legend for figure 1.

in which a portion of myocardium depolarizes early its potential does not have its usual phase relationships to other potentials. Premature depolarization of an area of musculature will produce surface electrocardiographic changes when the electrical discharge is sufficiently out of phase from other voltages large enough to obscure it and when its voltage is of sufficient magnitude not to be lost in transmission to the surface. Minor degrees of premature depolarization or discharges of low amplitude may not be readily apparent at conventional sensitivity of 10 mm. per millivolt.

Electrocardiographic tracings recorded with high amplification suggest that there is normally an overlap of atrial and ventricular potentials in the "P-R segment" which is not apparent in tracings recorded at conventional amplification.[1] Figure 6 demonstrates the relationship of surface "P-R segment" and QRS changes to the time difference between generation of atrial potentials and right ventricular depolarization. Changes in the initial part of QRS complexes may be due to superimposition of atrial potentials and initial forces of ventricular depolarization as "fusion beats."[2] This mechanism may produce surface Q waves. Myocardial infarction has been attributed to these changes in isolated beats by other authors.[3-6] This seems unlikely in the present cases in view of lack of clinical, historical, or postmortem evidence of infarction and the frequency with which these changes occur during catheterization. It is possible, however, that an infarction could produce electrical asynchrony as shown in figure 5, or the electrical and mechanical asynchrony associated with premature depolarization as shown in figures 2, 3, 4, and 7, and thus cause the initial QRS abnormalities in surface leads usually associated with infarction.

During premature ventricular depolarization the depolarizing potential is shifted from its customary locus producing changes in the terminal portions of the QRS and ST-T wave. The secondary ST-T-wave changes, demonstrated in figure 6, have a constant relationship to the time interval between premature ventricular and atrial depolarization. The mechanisms of production of surface lead abnormalities in positive two-step exercise or Master's tests may be due to the time difference between atrial and ventricular depolarization. It is conceivable that premature ventricular depolarization of an area of myocardium may occur during exercise tests.

Summary

Surface "fusion beats," beats with initial and terminal QRS abnormalities, and accompanying secondary ST-T-wave changes appear following intracavitary evidence of premature depolarization. In instances of premature activation of a portion of myocardium, the intracavitary deflection of premature ventricular depolarization may not be apparent in surface leads and, if present, may be reflected in surface leads only by subtle changes in wave configuration that include (1) shortening of the P-R interval, (2) prolongation or amplitude changes or both in the QRS, (3) changes in contour of initial and terminal portion of the QRS, sometimes resembling those of infarction, and (4) secondary ST-T-wave changes. Evidence of electrical asynchronism in a single ventricle and between ventricles is presented.

Acknowledgment

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Man Has Three Separate States of Existence

Some Divines count Adam thirty years old at his Creation, because they suppose him created in the perfect age and stature of man. And surely we are all out of the computation of our age, and every man is some months elder than he bethinks him; for we live, move, have a being, and are subject to the actions of the elements, and the malice of diseases, in that other World, the truest Microcosm, the Womb of our Mother.—Sir Thomas Browne. *Religio Medici.* Edited by W. A. Greenhill, M.D. London, Macmillan and Co., Ltd., 1950, p. 63.

Estimation of Flow Through Bronchial-Pulmonary Vascular Anastomoses with Use of T-1824 Dye

By H. W. Fritts, Jr., M.D., P. Harris, M.D., C. A. Chidsey III, M.D., R. H. Clauss, M.D., and A. Cournand, M.D.

IN ANIMALS the bronchial blood flow amounts to only a hundredth part of the output of the left ventricle,[1-3] and there is little reason to believe that this proportion is greatly different in normal man.[4, 5] But in certain diseases, particularly bronchiectasis, the bronchial vessels widen, and large anastomoses connect them with branches of the pulmonary artery and veins.[6-22] By conveying blood into the pulmonary circulation, these anastomoses can cause the output of the left ventricle to exceed that of the right.[23-29] Thus, if the outputs of the ventricles are individually measured, the anastomotic flow can be calculated as the difference between the two. This procedure will obviously not account for the entire bronchial circulation. It will, however, estimate that portion thought to show the largest increase in disease.

The first purpose of this paper is to describe a method for estimating the individual outputs of the ventricles when the flow from the left is larger than that from the right. This method, based on the Stewart-Hamilton dilution principle, entails injecting T-1824 dye into the venous circulation and inscribing simultaneous dilution curves from the pulmonary and brachial arteries. Earlier studies established the feasibility of this approach for estimating the output of the right ventricle in normal subjects.[30, 31] In the present study, the use of this principle for measuring anastomotic flow was first validated in models, then applied to patients in whom such flow was thought to exist.

The second purpose is to consider the effect of these anastomoses on the conventional Fick calculation of cardiac output. When the flows from the two ventricles are unequal, the Fick equation, yielding a single number, can obviously not measure both.[32]

Methods

Validation of the Method in Models

The models used to validate the method are sketched in figure 1. Each comprised three bead-filled chambers with volumes approximating, respectively, those of the right heart, the pulmonary vessels, and the left heart. Centrifugal pumps perfused the chambers with water.

Model A was designed to investigate whether dilution curves would measure the individual outputs of the ventricles when the output of the left exceeded that of the right by a known amount of extra flow. To eliminate the effect of recirculation of dye into the pulmonary vessels, the extra flow was delivered by an auxiliary channel equipped with a valve. In each experiment dye was injected into the vena cava, and dilution curves were drawn simultaneously from the pulmonary and brachial arteries. The procedure was repeated with the valve set at from five to 10 different positions.

Model B was similar to A except that the extra flow was derived from the aorta and was recirculated into the pulmonary vessels through a channel of adjustable length. This arrangement afforded an opportunity for studying the effect of recirculation on the brachial arterial dye curve. In each experiment dye was injected and curves were drawn as in the studies with the first model. The procedure was repeated with recirculation channels of various lengths.

The curves were inscribed with Colson densitometers[33] and analyzed according to the method of Hamilton.[34] The calculated flows were compared to those measured with flowmeters.

Application of the Method to Human Subjects

Each patient was studied in the postabsorptive basal state. None received premedication.

From the Department of Medicine, Columbia University, College of Physicians and Surgeons, and the Cardio-Pulmonary Laboratory of the First Medical and Chest Services, Columbia University Division, Bellevue Hospital, New York, New York.

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Table 1

Comparison of Actual and Calculated Right and Left Ventricular Flows Recorded in a Typical Experiment with Use of Model A. Each Number Is the Ratio of the Right to the Left Ventricular Output

Actual	Calculated
1.00	1.06
1.00	.95
.91	.93
.90	.88
.83	.81
.69	.72
.64	.62

One no.-9 cardiac catheter was advanced until its tip lay in the main pulmonary artery, and a second no.-9 catheter was advanced until its tip lay in the superior vena cava near the mouth of the right atrium. A Cournand needle was inserted into the right brachial artery.

Each study included from two to four breathing periods. The first served to wash out the open-circuit breathing apparatus with the patient's expired air, while the subsequent periods provided comparisons between the flows measured with the two dye curves and the Fick. During each of these last periods, the subject breathed quietly into the mouthpiece for 8 minutes before 4 ml. of T-1824 dye were injected into the catheter lying in the superior vena cava. Coincident with the injection, blood was sampled through two Colson densitometers connected to the catheter in the pulmonary artery and to the needle in the brachial artery. The blood and gas samples necessary for the Fick calculation were then collected. In alternate periods, the sequence of dye and Fick measurements was reversed.

The concentration of dye in plasma was read in a Beckman Model DU spectrophotometer. The curves were calibrated by use of the pooled-sample method of McNeeley and Gravallese.[35]

Subjects

Twenty-seven subjects were studied. These can be divided into four groups:

Normal Subjects

This group comprised nine convalescent patients believed to have normal hearts and lungs.

Patients with Bronchiectasis

This group included 11 patients with histories of long-standing bronchial infections. Bronchograms were obtained in nine of the patients and in each case confirmed the diagnosis.

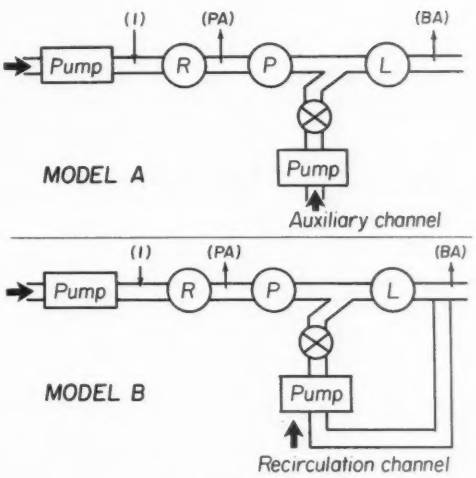

Figure 1

Schematic drawings of the models used to validate the method. R. P, and L are bead-filled chambers representing, respectively, the vascular volumes of the right heart, the lungs, and the left heart. Point of dye injection (I) and points of inscription of pulmonary (PA) and brachial (BA) arterial curves are indicated.

Patient with a Ligated Pulmonary Artery

This woman had had her left main pulmonary artery ligated at the time of a left upper lobectomy performed 9 months before the study.

Patients with Pulmonary Tuberculosis

This group consisted of six patients with long histories of pulmonary tuberculosis. Although the symptoms and clinical signs varied, all of the patients had x-rays compatible with far-advanced cavitary or fibrotic disease.

Results

Experiments in Models

The results obtained with Model A demonstrated that the method gave an estimate of the output of each ventricle that corresponded closely to the actual flow. Table 1 presents the results of a single experiment typical of those obtained in 10 such studies. It will be noted that each calculated ratio of the two ventricular outputs agreed with the actual ratio within 6 per cent.

The results of the experiments with Model B indicated that the length of the channel through which water recirculated was of criti-

Table 2

Values of Fick ($\dot{Q}_F$), Right Ventricular ($\dot{Q}_R$), and Left Ventricular ($\dot{Q}_L$), Flows Recorded in the Four Groups of Patients

Subject	$\dot{Q}_F$ (L./min.)	$\dot{Q}_R$ (L./min.)	$\dot{Q}_L$ (L./min.)	$\frac{\dot{Q}_L-\dot{Q}_R}{\dot{Q}_L}\times 100$ (%)
Group A—normal subjects				
F. M.	5.1	6.3	6.2	− 2
	4.8	5.6	5.6	0
	6.4	5.9	5.6	− 5
F. Mc.	7.7	7.2	8.5	+15
	7.0	9.2	8.8	− 5
J. D.	7.8	8.8	7.9	−11
	8.6	8.8	9.6	+ 8
L. S.	5.9	5.7	5.6	− 2
	6.3	7.0	7.0	0
S. G.	7.1	5.8	6.0	+ 3
	6.8	5.9	6.0	+ 2
A. M.	7.8	7.1	7.5	+ 5
	7.6	8.7	8.1	− 7
		8.0	7.3	−10
A. C.	7.1	7.2	8.3	+13
		8.2	10.6	+23
J. M.	8.3	7.5	6.7	−12
		4.6	4.7	+ 2
R. S.	4.6	5.2	5.2	0
Group B—patients with bronchiectasis				
H. C.	4.1	4.3	4.7	+ 9
	4.0	4.3	4.4	+ 2
	3.8	3.7	3.8	+ 3
G. M.		5.9	7.5	+21
		5.8	6.8	+14
		6.0	6.6	+ 9
P. W.	6.1	5.7	8.6	+34
	6.1	5.5	8.4	+35
J. St.	7.1	7.9	7.2	−10
		8.7	7.9	−10
M. B.		6.9	8.7	+21
	10.7	8.2	8.6	+ 5
	9.6	10.3	9.6	− 7
D. J.	7.0	7.2	7.9	+ 9
	7.5	8.0	10.5	+24
J. Sa.	6.3	6.3	6.1	− 3
	6.0	5.3	5.5	+ 4
W. Z.	5.4	5.4	5.4	0
		9.2	10.8	+15
A. B.		6.2	7.5	+17
		7.5	8.5	+12
C. S.		7.2	7.8	+ 9
		5.7	6.8	+24
D. W.	5.1	5.3	5.1	− 4
Group C—patient with ligated left pulmonary artery				
C. H.	6.1	6.1	7.9	+23
	5.3	6.2	7.5	+17
Group D—patients with tuberculosis				
I. C.	5.9	6.2	5.6	−11
	5.3	5.7	5.0	−14
	5.6	4.9	5.1	+ 4
B. S.	5.4	4.6	4.7	+ 2
	4.4	4.8	4.6	− 4
	4.8	3.8	4.6	+17
N. W.	3.3	3.1	2.9	− 7
	3.8	3.0	3.1	+ 3
	3.7	3.3	3.2	− 3
C. C.	4.5	4.1	4.2	+ 2
	4.3	3.5	4.4	+20
	4.8	4.0	4.7	+15
J. S.	6.0	5.4	5.3	− 2
	6.0	5.5	6.7	+18
F. B.	4.3	3.1	3.2	+ 3

cal importance. If the channel were too short, dye re-entered the pulmonary vessels rapidly and interfered with the downslope of the brachial arterial curve. This had the expected effect of reducing the calculated output of the left ventricle, and thus underestimating the flow through the bronchial-pulmonary anastomosis. Provided the channel of recirculation was long enough to prevent such contamination, however, the estimates of the individual ventricular outputs were as satisfactory as those obtained with Model A.

Studies in Human Subjects

Three comparisons of the dilution flows from the two ventricles were obtained in nine subjects, two in 15, and one in three. These results are presented in table 2 and are depicted graphically in figure 2.

In the normal subjects the output of the left ventricle was, on the average, 0.9 per cent larger than that of the right. Considerable variation was observed, however, in the individual patients. The largest discrepancy (subject A.C.) was 23 per cent.

In the patients with bronchiectasis, the average difference between the outputs was 9.7 per cent, a difference that would have

occurred by chance less frequently than 1 in 50 times ($t = 2.56$; D.F. = 41; $0.02>P>0.01$). This statistic must be interpreted with caution, however, because the data are weighted by the fact that the same number of runs were not completed in each case.

Two series of measurements were completed in the patient with the ligated pulmonary artery. In both, the output of the left ventricle exceeded that of the right by approximately 20 per cent.

In the patients with advanced pulmonary tuberculosis, the output of the left ventricle was on the average 2.9 per cent larger than that of the right. This figure was not significantly different from the average obtained in the normal subjects ($t = .586$; D.F. = 32; $P>.50$).

The agreement of the Fick flow with that calculated from each of the dye curves is depicted for all four groups of subjects in figures 3, 4, and 5. In the normal subjects and the patients with tuberculosis, the Fick results agreed satisfactorily with either ventricular flow. But in the patients with bronchiectasis and the woman with the ligated pulmonary artery, the Fick figures agreed best with the output of the right ventricle.

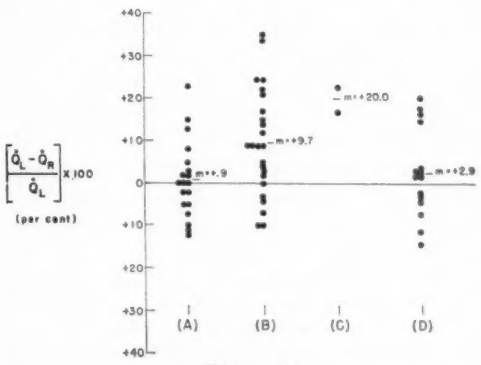

Figure 2

Difference between the left ($\dot{Q}_L$) and right ($\dot{Q}_R$) ventricular outputs expressed as a percentage of $\dot{Q}_L$. (A), normal subjects; (B), patients with bronchiectasis; (C), patient with a ligated pulmonary artery; and (D), patients with pulmonary tuberculosis. m indicates mean value.

Discussion

In contrast to the large number of studies carried out in animals, only a few attempts have been made to estimate the volume of blood carried by the bronchial vessels in man. Bing, Vandam, and Gray[23-25] estimated the flow entering the precapillary segments of the pulmonary vessels in patients with congenital heart defects. For this purpose they applied a modified version of the Fick principle. Gray, Lurie, and Whittemore[26] employed a similar approach in patients with chronic pulmonary disorders. Madoff, Gaensler, and Streider,[27] using the bronchospirometric method devised by Bloomer and his colleagues[29] for studying animals, estimated the precapillary flow into the pulmonary vessels of the right lung in a patient with congenital aplasia of the right pulmonary artery. More recently, Fishman, Turino, Brandfonbrener, and Himmelstein[28] employed bronchospirometry in combination with occlusion of one branch of the pulmonary artery to assess the precapillary contribution of the bronchial vessels in patients with either congenital heart defects or pulmonary disease. An earlier report[32] from this laboratory described the application of the indicator-dilution method to the estimation of anastomotic flow, presented the results obtained in patients with pulmonary disorders, and discussed the importance of this flow on the value of cardiac output calculated by the direct Fick equation. Subsequently, Cudkowicz and his co-workers[36] substituted radioactive iodine for dye, studied similar groups of patients, and obtained comparable results.

The validity of the present method rests on three major assumptions: (1) that the accuracy of the technic is sufficient to measure the quantities involved; (2) that the circulation times through the bronchial-pulmonary anastomoses are sufficiently long to prevent contamination of the downslope of the brachial arterial curve with recirculated dye; and (3) that the direction of flow through the anastomoses is from the bronchial vessels into the pulmonary bed.

The importance of the first of these three questions is emphasized by the results in the

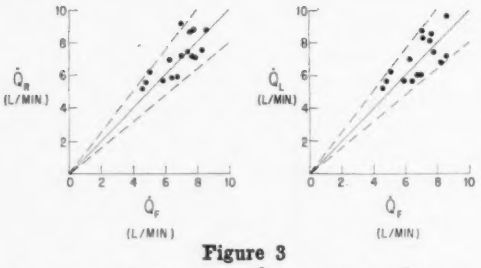

Figure 3

Agreement of the right ($\dot{Q}_R$) and left ($\dot{Q}_L$) ventricular outputs with the Fick ($\dot{Q}_F$) output in the normal subjects. Diagonal line indicates perfect agreement; dashed lines indicate differences of ± 20 per cent.

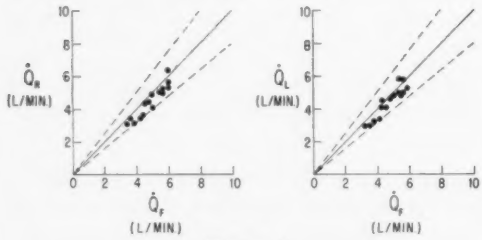

Figure 4

Agreement of the right ($\dot{Q}_R$) and left ($\dot{Q}_L$) ventricular outputs with Fick ($\dot{Q}_F$) output in the patients with pulmonary tuberculosis. Diagonal line indicates perfect agreement; dashed lines indicate differences of ± 20 per cent.

group of normal subjects. Although the average value for the left ventricular output exceeded that of the right ventricular output by only 0.9 per cent, there was considerable variability in the relationship of the two flows. Thus, there is little reason to expect the dye-dilution method to measure differences in the region of 1 per cent in any individual subject, and the application of the method to this problem must necessarily be on a statistical basis. At the beginning of the studies we had hoped that the present procedure would provide a more accurate comparison between the two outputs because it eliminated two major sources of discrepancy between duplicate measurements made by the conventional technic. In the first place, the flows are measured simultaneously, thus minimizing the effects of any minute-to-minute variations in cardiac output. Secondly, the amount of injected dye is common to both curves and inaccuracies arising from errors in measuring the amounts delivered are avoided. To investigate further the errors inherent in the method, five additional subjects were studied by inscribing in each three sets of simultaneous curves from the two brachial arteries after injecting dye into the axillary vein. Although on the average there was no difference between the two estimates, there was a discrepancy in one subject of 12 per cent. Such a discrepancy must be due to errors in sampling, analysis, and graphical calculation, and these errors must also apply to the present double dye-dilution technic.

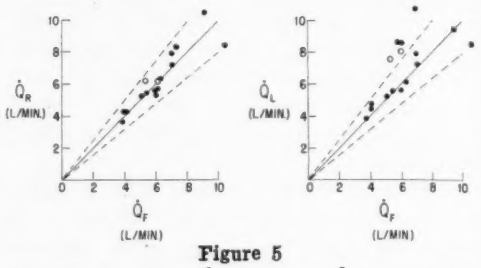

Figure 5

Agreement of right ($\dot{Q}_R$) and left ($\dot{Q}_L$) ventricular outputs with Fick ($\dot{Q}_F$) output in the patients with bronchiectasis (closed circles) and the patient with a ligated pulmonary artery (open circles). Diagonal line indicates perfect agreement; dashed lines indicate differences of ± 20 per cent.

The second important doubt as to the validity of the method concerns the recirculation time through the bronchial circulation and bronchial-pulmonary anastomoses. The experiments with Model B demonstrated that rapid rates of recirculation alter the downslopes of the brachial arterial curves and thus affect the estimates of the left ventricular output. Whether such contamination of the primary curve from the brachial artery occurred in the subjects studied is uncertain. The downslopes of these curves, however, did not show any early deviations from a linear exponential extrapolation. Moreover, if recirculation were present, the difference between the two dye-dilution flows would have been minimized, so that the validity of any positive evidence of bronchial-pulmonary shunts would not be affected.

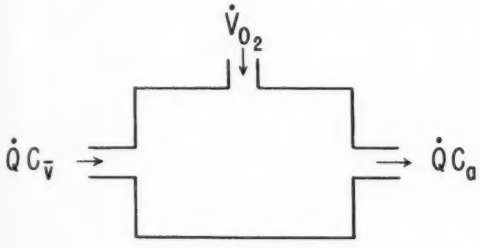

Figure 6

Schema of the normal pulmonary circulation in which bronchial-pulmonary anastomoses are unimportant. The symbols are defined in the text.

The third assumption concerns the direction of flow through the anastomoses. Others,[23-29] using variations of the Fick principle, have adduced evidence that blood flows through the anastomoses into the pulmonary vessels, and, although the dilution technic involves a different principle, our results are similar to those that they obtained. While evidence for a reversal of flow has been recorded in certain patients,[37] the pressure relationships in the systemic and pulmonary circulations suggest that such a reversal would be exceptional.

All three of these reservations about methodology appear to have been unimportant in the comparison of the group of normal subjects with the group of patients with bronchiectasis. Here the results show an increase in the estimated flow through the bronchial-pulmonary anastomoses which appears unlikely to have arisen by chance. It is in this group of patients that the presence of such anastomoses would be particularly expected. Further confirmation that such shunts existed is provided by the measurements made in one of our subjects (P.W.), who had severe unilateral bronchiectasis. After pneumonectomy he exhibited a reduction in the calculated anastomotic flow (table 3). Ligation of the pulmonary artery has also been shown to cause bronchial-pulmonary anastomoses to develop both in man[27, 38-42] and in animals,[29, 43-46] and in the woman with the ligated vessel, the results suggested an anastomotic shunt. Pulmonary tuberculosis is not a disease in which such anastomoses invariably develop, and again our observations are consistent with the known morbid anatomy.[19]

It remains to consider the relationship of these observations to the value of pulmonary blood flow provided by the Fick calculation. A formal treatment of this relation has been published previously.[32] In brief, the normal pulmonary circulation can be represented by the schema shown in figure 6, and the relation between the three streams of oxygen may be expressed as shown below:

$$\dot{V}_{O_2} = \dot{Q}\,C_a - \dot{Q}\,C_{\bar{v}} \qquad (1)$$

where

$\dot{V}_{O_2}$ = average rate of oxygen uptake (L./min.)

$\dot{Q}$ = average flow from the left and right ventricles (L./min.)

C_a = concentration of oxygen in an arterial specimen (L./L.)

$C_{\bar{v}}$ = concentration of oxygen in a mixed venous specimen (L./L.)

In the presence of bronchial-pulmonary anastomoses, the schema must be altered (fig. 7), and equation (1) must be expanded to include the effect of the anastomotic flow. Thus:

$$\dot{V}_{O_2} = (\dot{Q}_R + \dot{Q}_B)\,C_a - \dot{Q}_R\,C_{\bar{v}} - \dot{Q}_B C_B \qquad (2)$$

where

$\dot{Q}_R$ = average flow from the right ventricle (L./min.)

$\dot{Q}_B$ = average flow through the anastomoses (L./min.)

C_B = concentration of oxygen in the bronchial anastomotic blood (L./L.)

In this equation the output of the left ventricle equals $\dot{Q}_R + \dot{Q}_B$, and, by grouping terms, the following relation is obtained.

$$\dot{V}_{O_2} = \dot{Q}_R\,(C_a - C_{\bar{v}}) + \dot{Q}_B\,(C_a - C_B) \qquad (3)$$

Finally, division of both sides by the arteriovenous oxygen difference converts the left-hand term to the conventional Fick equation. Thus:

$$\dot{Q}_{FICK} = \dot{Q}_R + \dot{Q}_B \left[\frac{C_a - C_B}{C_a - C_{\bar{v}}}\right] \qquad (4)$$

Equation (4), which holds whether the bronchial-pulmonary anastomoses occur at precapillary, capillary, or postcapillary levels, indicates that the Fick calculation repre-

Table 3

Patient (P.W.) with Unilateral Bronchiectasis Studied before and after Pneumonectomy

	$\dot{Q}_T$ (L./min.)	$\dot{Q}_R$ (L./min.)	$\dot{Q}_L$ (L./min.)	$\frac{\dot{Q}_L - \dot{Q}_R}{\dot{Q}_L} \times 100$ (%)
Preoperative	6.1	5.7	8.6	+34
study	6.1	5.5	8.4	+34
Postoperative study	5.4	4.9	5.9	+17

Table 4

Theoretical Relation between the Fick Calculation ($\dot{Q}_F$) and the Individual Outputs of the Ventricles

When	Then $\dot{Q}_F$ equals
$C_B = C_{\bar{v}}$	Output of left ventricle
$C_{\bar{v}} < C_B < C_a$	Number larger than output of right ventricle but smaller than output of left
$C_B < C_{\bar{v}}$	Number larger than output of left ventricle
$C_B = C_a$	Output of right ventricle

sents the sum of two components: (a) the output of the right ventricle, and (b) an additional quantity, which may or may not equal the flow $\dot{Q}_B$ entering the pulmonary vessels from the bronchial-pulmonary shunts. This second component will equal $\dot{Q}_B$ when $C_B = C_{\bar{v}}$; it will be smaller than $\dot{Q}_B$ when $C_{\bar{v}} < C_B < C_a$; it will be greater than $\dot{Q}_B$ when $C_B < C_{\bar{v}}$; and it will be zero when $C_B = C_a$. Thus, as summarized in table 4, the correspondence of the Fick estimate and the output of either ventricle depends on the relation between the concentrations of oxygen in the blood in the systemic arteries, the pulmonary artery, and the bronchial-pulmonary anastomoses. The same general principle applies to any pathway carrying blood into the pulmonary vessels from sources other than the pulmonary artery. It may, therefore, be important in patients with Laennec's cirrhosis, because shunts between the portal and pulmonary circulations have been demonstrated in this disease.[47]

As shown in figures 3 and 4, the Fick agreed within 20 per cent with the dilution outputs of the two ventricles both in the normal subjects and in the patients with

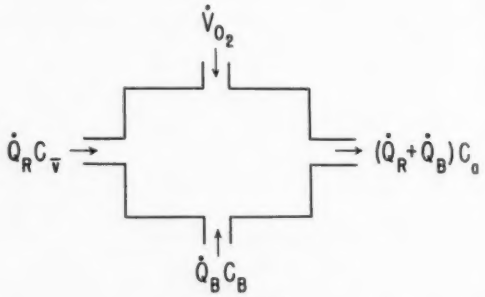

Figure 7

Schema of the abnormal pulmonary circulation with bronchial-pulmonary anastomoses present. The symbols are defined in the text.

tuberculosis. But this correspondence obtained in the patients with bronchiectasis and the woman with the ligated pulmonary artery only for the right ventricular flow (fig. 5). In these two groups the dilution flow from the left ventricle was larger than the Fick value in five of 16 measurements, suggesting that the concentration of oxygen in the blood flowing through the anastomoses must have been close to that in the systemic arterial blood. Once again this is in keeping with observations of the morbid anatomy, since the anastomoses appear to arise from the bronchial arteries, rather than the bronchial veins.[15]

Summary

A dye-dilution method devised to estimate the individual outputs of the ventricles has been used to assess the magnitude of the flow through bronchial-pulmonary anastomoses in patients with chronic lung disease. In 10 normal subjects the output of the left ventricle was, on the average, 0.9 per cent larger than the output of the right. In six patients with advanced pulmonary tuberculosis, the average value was 2.9 per cent, and in 11 patients with bronchiectasis 9.3 per cent. One patient, who had had her left main pulmonary artery ligated, exhibited an anastomotic flow of 20 per cent. In all groups the flow calculated from the Fick equation agreed within 20 per cent with that from the right ventricle. In the normal subjects and the patients with tuberculosis, the same general

agreement between the Fick and the left ventricular output was observed. But in the patients with bronchiectasis and the woman with the ligated pulmonary artery, the Fick calculation underestimated the left ventricular output. This underestimation suggests that the blood traversing the bronchial-pulmonary anastomoses had an oxygen content approximating that in the systemic arterial blood.

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Belief begins where science leaves off and ends where science begins.—VIRCHOW

Origin of Both Great Vessels from the Right Ventricle

I. Without Pulmonary Stenosis

By HENRY N. NEUFELD, M.D., JAMES W. DUSHANE, M.D., EARL H. WOOD, M.D., JOHN W. KIRKLIN, M.D., AND JESSE E. EDWARDS, M.D.

AMONG the congenital malformations in which an abnormal relationship exists between the aorta and pulmonary trunk is that in which both of these vessels arise from the right ventricle. The only outlet for the left ventricle is a ventricular septal defect. Right ventricular infundibular stenosis may or may not be associated. These cases apparently are extremely rare,[1-3] and only a few have been reported in the last 25 years.[4-7] A few cases were documented in the last century.[1, 3]

Many terms have been used for this malformation, including "partial transposition,"[2] "double-outlet right ventricle,"[7] and "origin of both great vessels from the right ventricle."[8]

Witham,[7] in 1957, summarized six cases reported in detail in the literature and added four cases. He divided these cases into two groups and called them the "Fallot type" and the "Eisenmenger type," depending on the presence or absence of pulmonary stenosis.

One of the patients in his study was seen at the Mayo Clinic.[9] This case was not included in the present analysis because additional multiple intracardiac malformations were present, and it appeared to us that different embryologic as well as hemodynamic problems were involved.

In a study of the pathologic and clinical material from the Mayo Clinic, we found 14 cases in which both great vessels originated from the right ventricle. Three main categories of this malformation occurred as follows: (1) without pulmonary stenosis (eight cases); (2) with pulmonary stenosis (five cases) and (3) with other intracardiac malformations (one case).

The purpose of this investigation is to correlate the anatomic findings (pathologicoanatomic or surgical) with the clinical and hemodynamic data and to discuss the possibilities of clinical diagnosis.

The three groups, although probably related embryologically, present different anatomic, clinical, hemodynamic, and surgical problems; therefore, we will discuss them in two separate communications.

The present paper is concerned with the eight cases of this malformation without pulmonary stenosis. The diagnosis in five instances was proved at necropsy, whereas it was established during operation in the other three. In two cases, patent ductus arteriosus, mitral insufficiency, and some degree of coarctation of the aorta were present. Pulmonary hypertension was present in all eight cases.

Pathologicoanatomic Features

The anatomic features in the five cases studied at necropsy fell into two subgroups that could be distinguished from each other by the relationship of the aortic and mitral valves. In the first subgroup (three cases), these two valves lacked the element of continuity found in normal hearts; the second subgroup (two cases) was marked by continuity between aortic and mitral valvular tissue.

In the first subgroup, the ascending aorta and the pulmonary artery appeared from the exterior to have a normal relationship, the ascending aorta lying to the right of the pulmonary trunk. The interior of the heart, however, revealed a profound abnormality of the aorta. Instead of extending inferiorly from the base of the heart to a position

From the Mayo Clinic and the Mayo Foundation, Rochester, Minnesota.

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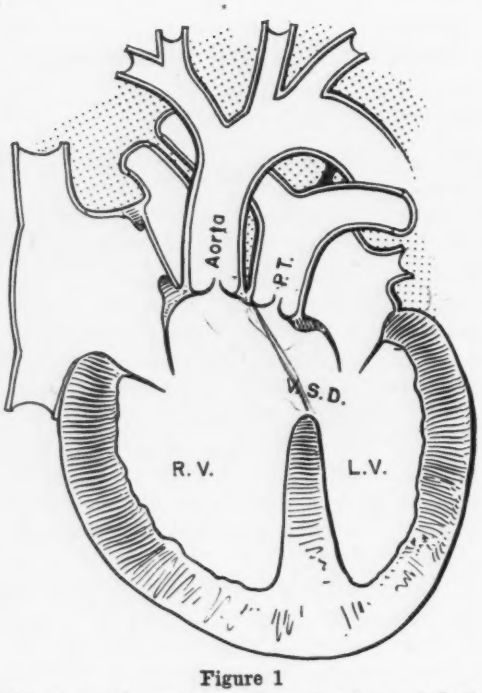

Figure 1

Diagrammatic representation of origin of both great vessels from right ventricle without pulmonary stenosis and with ventricular septal defect.

dorsal and caudal to the pulmonary valve, the aortic orifice communicated only with the right ventricle and lay to the right of and in the same coronal body plane as the pulmonary valve (figs. 1 and 2).

The interior of the right ventricle showed a prominent horizontal crista supraventricularis, with the aortic orifice lying between two branches of this structure. A ventricular septal defect was present in the basal part of the septum, caudal to the crista supraventricularis. Dorsally, this defect was bounded by the junction of the anterior mitral leaflet and the septal tricuspid leaflet. The caudad, ventral, and cephalad edges of the defect were composed of muscle; the muscle forming the cephalad boundary was the crista supraventricularis. By means of right ventricular landmarks, the position of the ventricular septal defect could be identified as lying dorsally and caudal to the crista supraventricularis and being caudal to the tricuspid valve.

The anatomic relationships of the mitral valve were abnormal because of the aforementioned lack of continuity between the aortic and mitral valves. Although the basal attachments of the posterior mitral leaflet were normal, those of the anterior leaflet were abnormal. The main basal attachment of the anterior mitral leaflet was to the septal tricuspid leaflet, with which, as already noted, it was continuous behind the septal defect. Anteriorly, the base of the anterior mitral leaflet attached to the muscle forming the superior boundary of the ventricular septal defect (fig. 3).

Two of the three hearts in this first subgroup corresponded to the above description. A second type in this first subgroup of cases was represented by one case (fig. 4). In this instance, the ventricular septal defect was cephalad to the crista supraventricularis and beneath the pulmonary valve. The aorta arose entirely from the right ventricle, being to the right of and slightly dorsal to the pulmonary valve. The aortic and pulmonary valves were in the same cross-sectional body plane. The ventricular septal defect was separated from the tricuspid valve by the crista supraventricularis, which lay in a horizontal position. The septal defect was surrounded on all sides by muscle. Dorsally, this muscle made up the left extremity of the crista supraventricularis.

The posterior mitral leaflet had normal attachments. The anterior mitral leaflet was attached to the posterior edge of the ventricular septal defect, being separated from the aortic valve and the tricuspid valve by the aforementioned muscle, which formed the posterior wall of the ventricular septal defect.

From the viewpoint of anatomic classification, it is of significance in these cases that, if an incision is made through the left ventricular wall into the aorta, one initially gains the impression that the aorta is in direct continuity with the left ventricle. However, this is an illusion since, in order to reach the aorta from the left ventricle, one must pass through the ventricular septal defect (fig. 5).

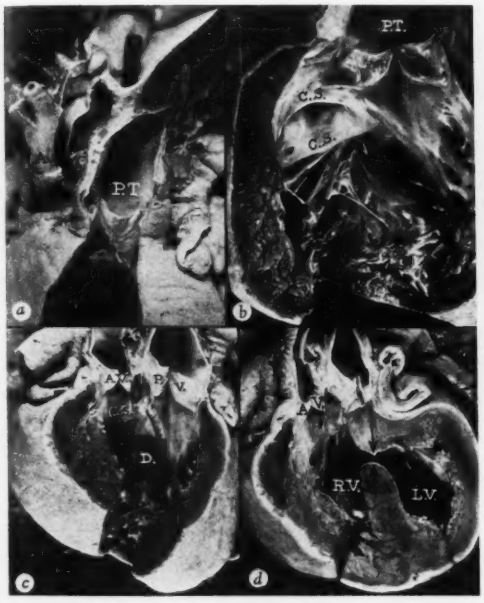

Figure 2

Case 3. First subgroup of origin of both great vessels from right ventricle without pulmonary stenosis and with ventricular septal defect. a. *Outflow portion of right ventricle and great vessels. The ascending aorta (A.) lies beside the pulmonary trunk (P.T.). Exteriorly, the relationship between the two great vessels did not appear abnormal. A probe lies in a patent ductus arteriosus.* b. *Interior of right ventricle and origin of pulmonary trunk (P.T.). Between the two limbs of the crista supraventricularis (C.S.) is a channel leading to the origin of the aorta. The ventricular septal defect lies below the lower limb of the crista.* c. *Interior of right ventricle in similar perspective to that in* b. *A sagittal section has been made through the valves and great vessels. The ventral limb of the crista supraventricularis has been removed, leaving the dorsal limb (C.S.). The aortic valve (A.V.) lies to the right of and in the same body plane as the pulmonary valve (P.V.). The ventricular septal defect (D.) lies dorsal to both the aortic and pulmonary valves and below the crista supraventricularis.* d. *Section made in right ventricle in* c *carried across ventricular septum and through lateral wall of left ventricle, exposing left ventricular cavity (L.V.). The ventricular septal defect lies between the arrows. It is the only outlet for the left ventricle and it leads directly into the right ventricle (R.V.).*

As already noted, the second subgroup of these five cases studied at necropsy comprises

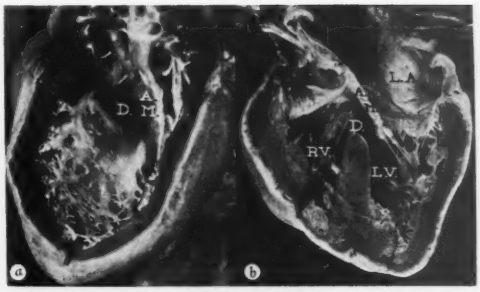

Figure 3

Case 3. Relationships of ventricular septal defect and mitral valve. a. *Interior of left ventricle. The only outlet for the left ventricle is the ventricular septal defect (D.). The anterior leaflet of the mitral valve (A.M.) forms part of the dorsal wall of the ventricular septal defect.* b. *Section through heart parallel to that shown in figure 2*d *but on a more dorsal plane that lies dorsal to the semilunar valves. The anterior leaflet of the mitral valve has continuity with the septal leaflet of the tricuspid valve (S.T.) behind the ventricular septal defect. The anterior leaflet of the mitral valve attaches anteriorly with the muscular edge of the ventricular septal defect and does not have continuity with the aortic valve. This is in striking contrast to the normal situation. L.A. = left atrium.*

the two cases in which the aortic and mitral valves were continuous. This normal relationship existed not by virtue of a normal position of the aortic valve but as the result of an unusually long anterior mitral leaflet. The latter ascended through the ventricular septal defect to join the aortic valve. The latter lay entirely over the right ventricle and to the right of the ventricular septal defect.

From the exterior, the relationships of the aorta and pulmonary trunk appeared to be normal (fig. 6). The interior of the right ventricle revealed a large ventricular septal defect dorsal to the horizontal crista supraventricularis. In the usual instance in which a ventricular septal defect lies dorsal to the crista, the defect also is caudal to the septal leaflet of the tricuspid valve. In these two cases, the relationship of the defect to the tricuspid valve was unusual. It was not related closely to the septal leaflet of the tricuspid valve but instead lay cephalad and medial to the commissure between the anterior

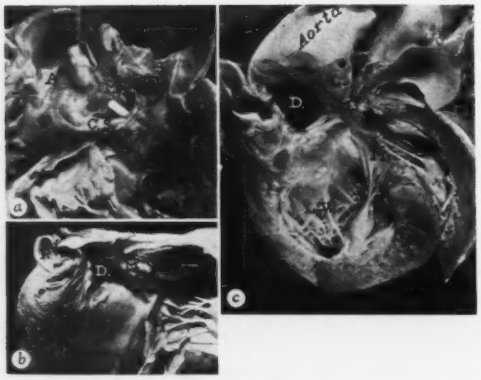

Figure 4

Case 5. a. *Right ventricular aspect viewed laterally. The ventricular septal defect (probe) lies above the crista supraventricularis and dorsocaudal to the pulmonary valve. The ventricular septal defect is surrounded on all sides by muscle; that forming the dorsal wall is designated by "M." The origin of the aortic valve lies dorsal to and to the right of the pulmonary valve but at the same cross-sectional body plane. The aorta originates entirely from the right ventricle and does not straddle the defect.* b. *Base of left ventricle viewed laterally. The ventricular septal defect (D.) lies behind the pulmonary valve (P.). The aortic valve lies beyond the ventricular septal defect and is separated from the anterior leaflet of the mitral valve (A.M.) by the muscle (M.), which forms the dorsal wall of the ventricular septal defect.* c. *Left ventricle, ventricular septal defect, and aorta. This perspective is the result of an incision made through the anterior wall of the left ventricle and carried into the aorta. The impression of continuity between the aorta and the left ventricle is an illusion. No continuity exists between aortic and mitral valves. The ventricular septal defect is surrounded on all sides by muscle, and the aortic origin lies on the right ventricular side of the ventricular septal defect. Interposed between the aortic valve and the anterior mitral leaflet (A.M.) is the mass of muscle (M.) that forms the dorsal wall of the ventricular septal defect. L. = left aortic cusp.*

and septal tricuspid leaflets. The defect in one case extended upward toward the right to lie cephalad to the major portion of the anterior tricuspid leaflet (fig. 6*a*).

Forming the lower dorsal boundary of the ventricular septal defect was the anterior leaflet of the mitral valve where it was continuous with the septal tricuspid leaflet.

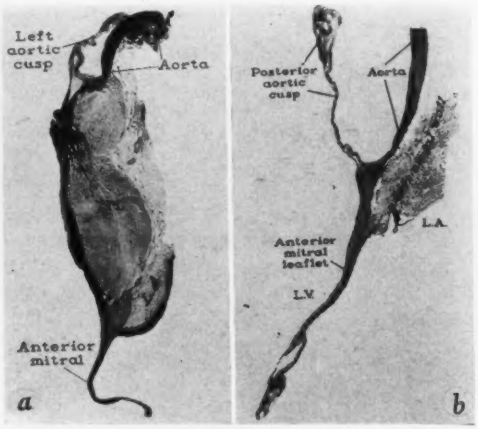

Figure 5

Case 5. a. *From case illustrated in figure 4. This low-power photomicrograph of a section made through the left aortic cusp and anterior mitral leaflets shows the mass of muscle (M.) interposed between the two valves. This muscle represents the dorsal wall of the ventricular septal defect and is abnormal in position. L.A. = left atrial wall.* b. *Section through aortic and mitral valves of normal heart in essentially the same plane for comparison with* a. *The normal heart shows continuity between aortic and mitral valves, in contrast to the abnormal heart.*

Cephalodorsally, the anterior mitral leaflet extended upward to form the cephalodorsal boundary of the ventricular septal defect, and then it joined the root of the aorta and the aortic valve.

When the left ventricular incision was extended into the aorta during dissection of these hearts, the incision cut through the elongated anterior mitral valve and aorta. Muscular tissue did not intervene between these two valvular structures (fig. 7), as was present in the second type of the first subgroup of hearts.

It might be asked justifiably how the hearts of the second subgroup differ from those with the common variety of ventricular septal defect. The following differences may be pointed out: In the hearts of this subgroup, the aorta does not connect directly with the left ventricle or straddle the ventricular septal defect; rather, it lies to the right of the defect. The aortic valve connects with the

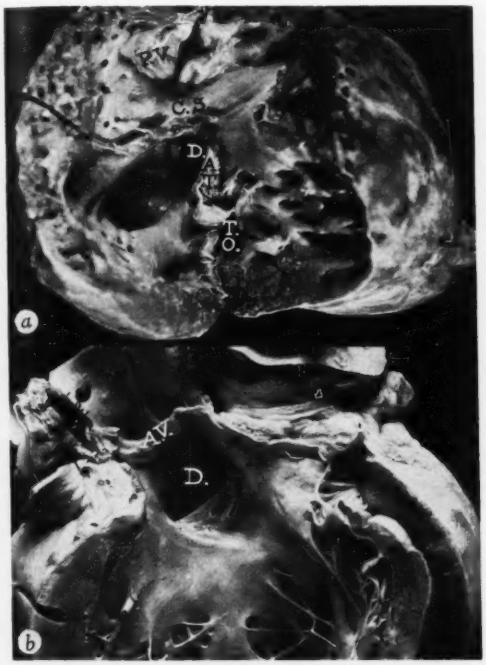

Figure 6

Case 1. Second subgroup of origin of both great vessels from right ventricle without pulmonary stenosis. a. *Interior of right ventricle. The ventricular septal defect (D.) is separated from the pulmonary valve (P.V.) by the horizontal crista supraventricularis (C.S.). The defect, although lying posteroinferior to the crista, has an abnormal relationship to the tricuspid valve, lying ventral to the anterior tricuspid leaflet (A.T.). The aortic valve lies immediately above the defect and communicates entirely with the right ventricle, although it has continuity with the anterior leaflet of the mitral valve.* b. *Left ventricle and aortic valve (A.V.). The dorsal wall of the ventricular septal defect (D.) is formed by the anterior leaflet of the mitral valve (A.M.) as it becomes continuous with the septal leaflet of the tricuspid valve below and with the aortic valve above. Continuity is present between aortic valvular tissue and tissue of the anterior leaflet of the mitral valve, but it does not result from a normal position of the aorta but rather because of an abnormally long anterior mitral leaflet, which ascends through the ventricular septal defect to become continuous with the aortic valve. An additional abnormality is that the portion of the heart in which the aortic and mitral valves are continuous has an epicardial relationship; in normal hearts, on the contrary, the zone of continuity between the mitral and aortic valves is entirely intracardiac.*

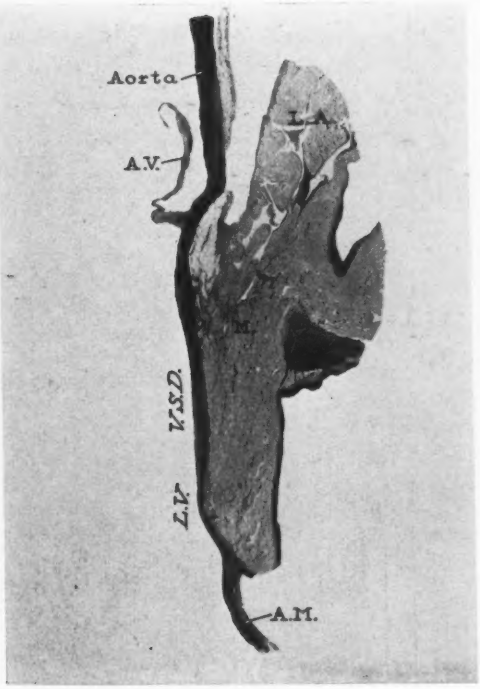

Figure 7

*Case 6. Low-power photomicrograph showing continuity between aortic valve and anterior leaflet of mitral valve. The relationship between the two valves is profoundly different from that in the first sub-group (fig. 5). Although the relationship in this case bears some similarity to the normal, the zone of continuity between the two valves has a close epicardial relationship. Under normal conditions, this zone is entirely in an intracardiac position. The recess between the aortic wall and the left atrial wall is the pericardial cavity. Contrast this with the normal in figure 5*b.

mitral valve not because of a normal position but because an elongated anterior mitral leaflet extends upward and to the right to join the aortic valve. The aortic valve is not caudal to the pulmonary valve but lies at the same level. The ventricular septal defect does not extend caudally dorsal to the septal tricuspid leaflet but rather extends cephalad ventral to the anterior tricuspid leaflet.

Clinical Findings

The clinical findings (table 1) were similar to those in cases of ventricular septal defect with associated pulmonary hypertension.

Table 1

Clinical Data in Eight Cases of Origin of Both Great Vessels from Right Ventricle

Case	Age, yrs.	Sex	History				Physical findings*					
			Cyanosis	Shortness of breath	Congestive failure	Respiratory infections	Systolic thrill, location	Systolic murmur, grade and location†	Other murmurs; type, grade and location	Second pulmonic sound	Blood pressure, mm. of Hg	Femoral pulses
1	14	F	−	+	−	+	LICS (2-4)	III (3)	−	+++ Split	98/68	+
2	4	F	−	+	+	+	Left sternal border	III (3-4)	Mid diastolic	+++ Split	92/60	+
3	15	F	−	+	−	+	LICS (2-3)	II (2-4)	SM, I, apex; DM, I, apex	++	110/60	+
4	6	M	When crying	+	−	+	Supra-sternal notch	III (3-4)	SM, I, apex	+++	94/60	±
5	2	M	−	−	−	−	LICS (3-4)	IV (3-4)	DM, apex	+++ Split	90/50	+
6	9	M	−	+	−	−	+	III (2-4)	DM, I, LICS (2-4)	+++	88/60	+
7	3	F	−	+	+	+	−	II (4)	−	+	94/50	+
8	2	M	Since age 3 mo. when crying	+	+	++	Lower sternum	III (4)	DM, I, apex	+ Split	95/45	+

*LICS, left intercostal space; DM, diastolic murmur; SM, systolic murmur.

†Roman numerals indicate grade of murmur; arabic numbers in parentheses indicate those left intercostal spaces where the murmur was heard.

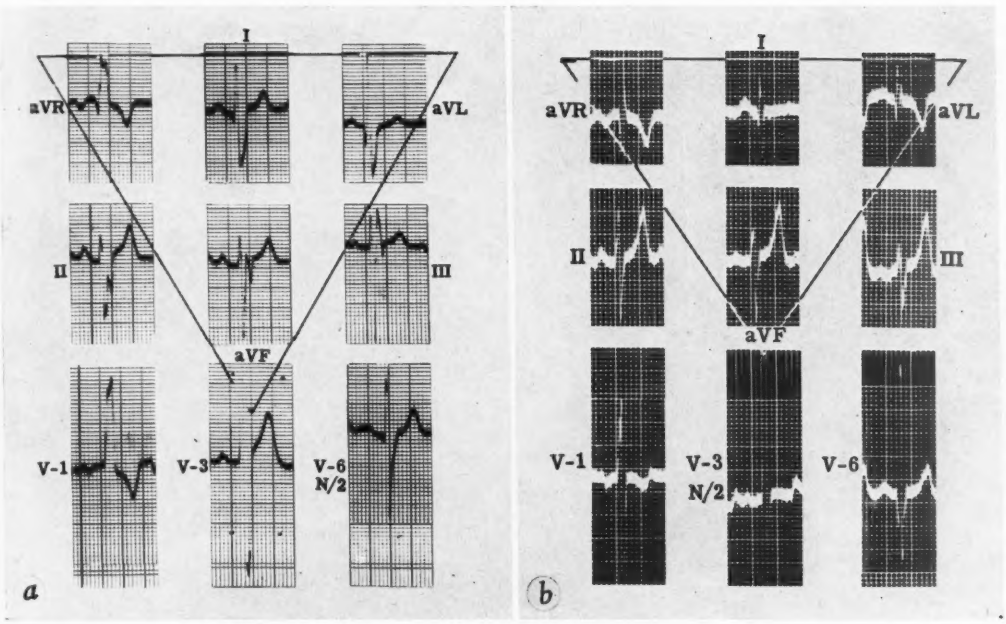

Figure 8

Electrocardiograms in two cases. a. *Case 1.* b. *Case 7. See table 2 for details.*

There were four boys and four girls, with ages ranging from 2 to 15 years.

Slight cyanosis had been noted after effort in two patients. All but one had experienced dyspnea after effort. In three patients, congestive heart failure had been present in the past or was noted at the time of observation. Six patients had a history of recurrent respiratory infection.

Examination at the clinic did not show cyanosis or clubbing in any of the patients. A systolic thrill was present in all but one patient. A systolic murmur was present in all eight cases, varying from grade II to grade IV (on the basis of grades I to VI established by the New York Heart Association).

A grade I apical diastolic murmur was heard in three patients, and two had a Graham Steell murmur. An apical systolic murmur suggesting mitral insufficiency was noted in two patients (cases 3 and 4); this lesion subsequently was found at necropsy. The second pulmonic sound was accentuated in all eight patients. Femoral arterial pulsations were palpable in all instances, being somewhat diminished in one patient (case 4) because of an associated coarctation of the aorta. The blood pressure was in the normal range in all patients.

Electrocardiographic Findings

All eight patients had normal sinus rhythm (fig. 8). The P-R interval was greatly prolonged in case 3 and slightly prolonged in all the other cases, as based on the assumed P-R interval for age and heart rate (Ziegler).[10]

The P waves were high and notched in leads I, II, and aV_F, suggesting left atrial enlargement, in the two patients (cases 3 and 4) in whom mitral insufficiency was found at necropsy.

The most striking electrocardiographic features in these eight cases were the manifest mean electric axes and the vectors of the QRS complexes in the frontal plane as projected from the scalar electrocardiograms (table 2). The manifest mean electric axes of the QRS complexes in seven of the patients

Table 2

Electrocardiographic Findings in Eight Cases of Origin of Both Great Vessels from Right Ventricle

Case	Age, yrs.	Rate, beats per min.	QRS axis, degrees	QRS vector loop, frontal plane*	P waves, mm.	P-R interval, sec.	QRS complex, sec.	QRS in lead V_1, mm.	R in aV_R, mm.	R:S ratio in aV_R	QRS in lead V_6, mm.
1	14	90	−160	CCL	High, notched; 3 mm. in I; 4 mm. in II	0.20	0.14	r R′ R′ = 22	10	>1	Q = 2 R = 13 S = 22
2	4	120	− 70	CCL	High; 3 mm. in II	0.16	0.08	R = 25	9.5	>1	Q = 2 R = 30 S = 4.5
3	15	83	−120	CCL	Notched in I, II and aV_F	0.24	0.12	r R′ R′ = 23	12	>1	Q = 2 R = 22 S = 9
4	6	112	−170	CCL; figure-of-eight	High and notched in I, II and aV_F	0.17	0.14	R = 25	8	>1	Q = 10 R = 28 S = 19
5	2	142	− 30	CCL	Notched in I and aV_F	0.16	0.07	RS R = 32 S = 14	2.5	<1	Q = 6 R = 20
6	9	100	−130	CCL	2 mm. in II	0.16	0.10	RS R = 25 S = 14	16	>1	Q = 4 R = 28 S = 18
7	3	120	− 90	CCL	Normal	0.16	0.08	RS R = 13 S = 17 Slurred R	12	>1	Q = 5 R = 27 S = 13
8	2	136	+120	CL	3 mm. in II	0.14	0.08	RS R = 33 S = 10	9	=1	Q = 12 R = 33 S = 6

*CCL, counterclockwise; CL, clockwise.

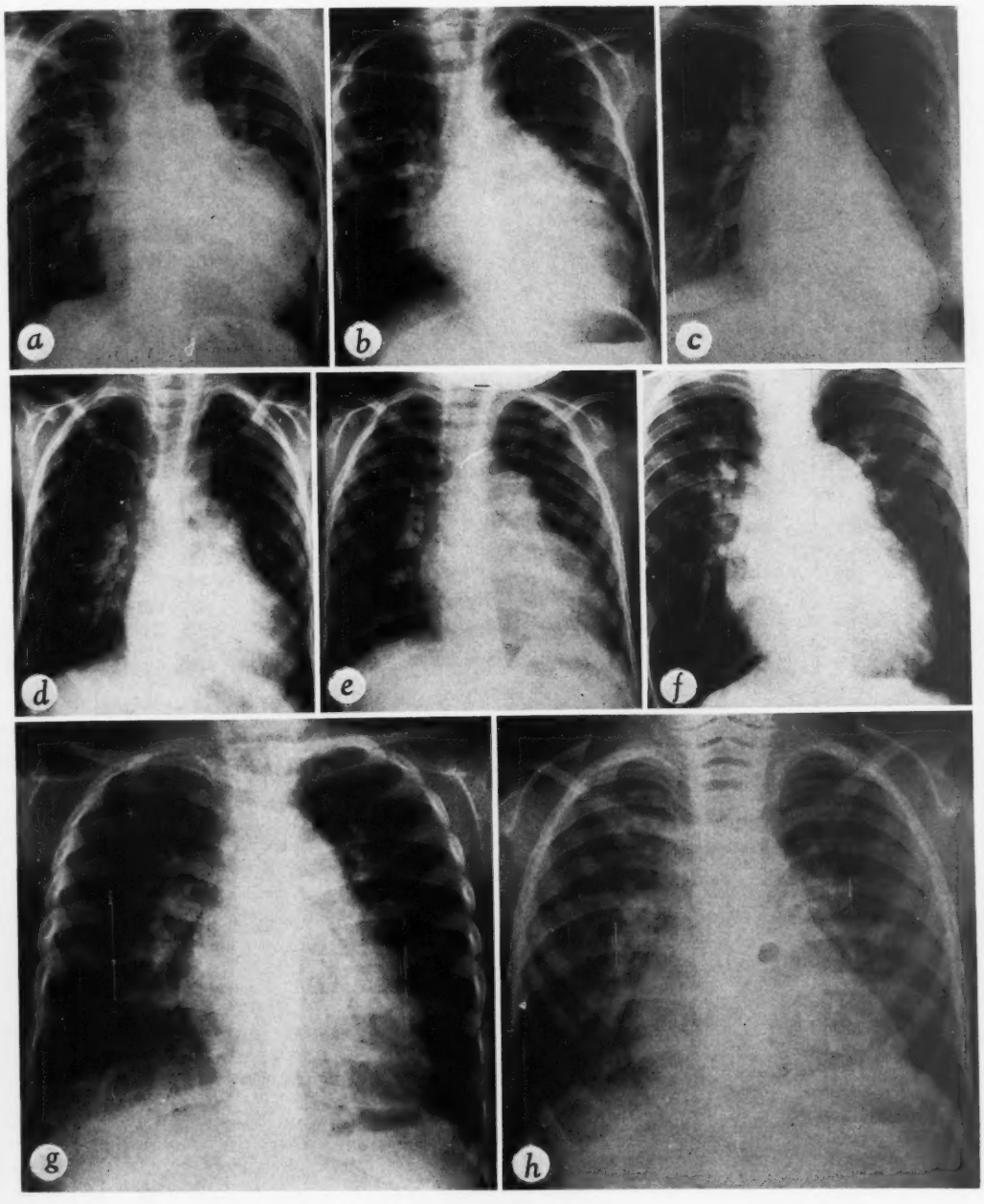

Figure 9

a-h. *Posteroanterior thoracic roentgenograms in cases 1 through 8, respectively. See text for details.*

Table 3

Hemodynamic Data in Eight Cases of Origin of Both Great Vessels from Right Ventricle

Case*		Pressure, mm. Hg†						Blood oxygen saturation, per cent‡						O_2 capacity, vol. per cent
		RA	RV	PA	Radial artery	Aorta	LA	IVC	MRA	SVC	RV	PA	Radial artery	
1	A	14/8	103/16	100/44	—	—	—	—	63	—	94	90	96.7 FA	17.4
	B	15/9	82/8	—	—	89/47	21/12							
2	(B)	8/5	85/6	—	—	LV 88/7	16/8							
3	(A)	9/3	110/15	110/68 135/75	119/54	102/60 via (ductus) 130/75	—	70	71	70	80	89	91	18.0
4	(A)	20/14	124/10	129/60	131/79	121/96	—	38	38	46	43	45	66	19.6
		—	80/70	—	—	LV 98/10	—							
5	(A)	4	70/5	60/15	—	70/40	—	—	50	50	80	80	89 Aorta	—
6	A	7	92/0	85/41	—	—	—	—	65	68	82	83	88	14.9
	B	9/6	75/6	74/23	73/47	—								
7	A	10/0	80/0	—	—	—	10/0							
	B	7	77/4	—	83/51 FA	—	19/9							
8	(B)	9/5	86/6	73/19	91/43	LV 119/8	—							

*A, catheterization performed elsewhere; B, data obtained during operation.
†RA, right atrium; RV, right ventricle; PA, pulmonary artery; LA, left atrium; LV, left ventricle; FA, femoral artery.
‡IVC, inferior vena cava; MRA, mid right atrium; SVC, superior vena cava.

lay between −30 and −170 degrees; the frontal QRS vector described a counterclockwise loop in seven of these patients, and its major portion was superiorly oriented. Only one patient (case 8) had a different vector and axis. All patients showed a certain degree of right ventricular hypertrophy. The R waves in lead V_1 were high in all instances. The R:S ratio in lead aV_R was 1 or more in seven patients (fig. 8).

A QRS or QR pattern was present in lead V_6 in all cases, with the Q waves ranging from 2 to 12 mm. (0.2 to 1.2 mv.), the R waves from 13 to 33 mm. (1.3 to 3.3 mv.), and the S waves from 4.5 to 22 mm. (0.45 to 2.2 mv.).

Roentgenologic Appearance

Roentgenologic examination revealed enlargement of the cardiac shadow and increased pulmonary vasculature as evidence of pulmonary arterial hypertension in all patients (fig. 9). In two instances (cases 1 and 8), the supracardiac shadow was widened.

Hemodynamics

The cardiac catheterization data are shown in table 3. In two of the patients (cases 3 and 4), complete data were obtained in our laboratory; case 3 will be discussed in greater detail. Most important is the fact that the pulmonary arterial pressure was equal to the systemic arterial pressure in all of the patients.

The peripheral systemic arterial oxygen saturation varied from slightly below normal (88 per cent) to normal (96.7 per cent) in four of the five patients in whom it was obtained, while the fifth patient (case 4) showed severe arterial hypoxemia. This patient had congestive heart failure and was studied while he was under anesthesia. Values for the oxygen saturation of pulmonary arterial blood were obtained in the same five patients; in two (cases 3 and 6), the values in the pulmonary artery and the aorta were closely similar.

Sufficient data were obtained in four patients to exclude the presence of a large left-to-right shunt at the atrial level.

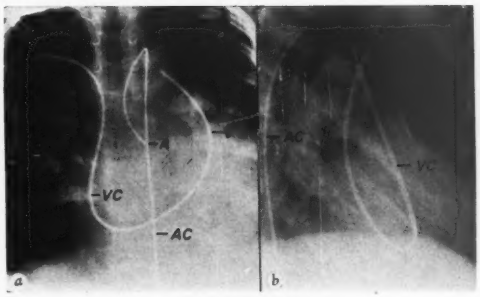

Figure 10

Case 4. a. *Position of catheter in posteroanterior view. VC = venous catheter; AC = aortic catheter; A = aortic valve; V = pulmonary valve. Note that both valves are at approximately the same level.* b. *Lateral view. Note that the distal part of the aortic catheter is positioned anterior to the venous catheter.*

Data in Case 3

The data obtained during cardiac catheterization in case 3 established the presence of an interventricular communication and an aorticopulmonic communication, the latter being interpreted as a patent ductus arteriosus. The catheter traversed the ductus on numerous occasions and was advanced into the abdominal aorta.

The oxygen saturation of right radial arterial blood (91 per cent) was 2 per cent greater than that of blood withdrawn simultaneously from the femoral artery. The oxygen saturation of femoral and pulmonary arterial blood apparently was identical. Dye-dilution curves recorded simultaneously at the right radial and femoral arteries after injection into the superior vena cava were similar, each showing a right-to-left shunt that was approximately 35 per cent at the radial artery and slightly greater at the femoral artery.

The pulmonary blood flow of 15.0 liters per minute was considerably greater than the systemic blood flow of 5.8 liters. The estimated pulmonary resistance of 380 dynes sec. cm.$^{-5}$ was significantly less than the total systemic resistance of 1035 dynes sec. cm.$^{-5}$.

The data were interpreted to indicate a large left-to-right shunt at the ventricular level. The identity of the oxygen saturation levels in the pulmonary and femoral arteries is compatible with the interpretation that partial or complete interruption of the aortic arch was present, with all, or a large portion, of the descending thoracic aorta originating from the ductus arteriosus. Partial interruption of the aortic arch was found at operation. The systolic pressure in the aortic arch was significantly higher than that in the descending aorta (table 4).

Table 4

Effect of Temporary Closure of Patent Ductus Arteriosus on Central Arterial Pressures (Case 3)

	Pressure, mm. Hg		
	Aortic arch	Descending aorta	Pulmonary artery
Ductus open	137/57	124/58	128/66*
Ductus closed	143/74	111/75	149/58*

*Pressures in pulmonary artery not recorded simultaneously with those in aorta.

Temporary closure of the ductus during operation resulted in a decrease in systolic pressure in the descending aorta and an increase in systolic pressure in the pulmonary artery, indicating the presence of a significant flow of blood via the ductus into the descending aorta (table 4).

This patient had practically uniform mixing of systemic venous and pulmonary venous blood in the outflow tract of the right ventricle and in the pulmonary artery, since the oxygen saturation of blood in the pulmonary, right radial, and femoral arteries was closely similar.

Discussion

The clinical picture in these patients was that of a large ventricular septal defect with pulmonary hypertension. Electrocardiography showed features that could be of some diagnostic help. To our knowledge, the electrocardiographic changes in this anomaly have not been previously described in detail. Witham[7] included an electrocardiographic tracing in one case of his "Eisenmenger group," but it is difficult from the reproductions to judge the exact portion of the electric axis and the vectorial QRS loop in the frontal plane; the axis was described as left and the P-R interval as being prolonged.

As already noted, all of our patients had prolonged P-R intervals, and the manifest mean electric QRS axis ranged between −30 and −170 degrees in all but one instance. The QRS loop as projected on the frontal plane rotated in a counterclockwise direction in six patients, and its major portion was superiorly oriented. The universal presence of right ventricular hypertrophy was indicated by the magnitude of the R waves in leads aV_R and V_1 and of the S waves in V_6. In cases 1, 3, and 4, a typical pattern of right bundle-branch block was observed.

The combination of the QRS electric axis lying above the superior point and a counterclockwise rotation of the QRS vector in the presence of signs of right ventricular hypertrophy has been described as an important electrocardiographic sign in persistent common atrioventricular canal by Toscano-Barboza and associates.[11] Toscano-Barboza and DuShane[12] found such electrocardiographic findings in nine of 59 anatomically proved cases of ventricular septal defect. According to Keith and co-workers,[13] and Char and associates,[14] the combination of left axis deviation in the standard leads and right ventricular hypertrophy in the precordial leads in cases with ventricular septal defect is rare.

Toscano-Barboza and associates,[11] in their explanation of the electrocardiographic changes in common atrioventricular canal, suggested that the defect at the top of the ventricular septum causes a fundamental alteration in the excitation pathway into the ventricles.

Neufeld and co-workers[15] found similar electrocardiographic alterations in excitation with ventricular septal defects of the persistent common atrioventricular canal type. Histologic studies showed that the conduction tissue lay dorsal to and skirted the ventricular septal defect. Similar changes were found by Lev[16] in cases of common atrioventricular canal.

Since the defect in cases in which both great vessels originate from the right ventricle is positioned dorsally, the same changes in the position of the conduction system might be expected. At present, these changes in conduction are thought to be on the same embryologic basis as the defect and are a possible cause of the electrocardiographic alterations.

In the presence of clinical signs of ventricular septal defect with pulmonary hypertension and the electrocardiographic changes already described, the possibility of both great vessels originating from the right ventricle should be considered, as well as the possibility of a ventricular septal defect of

the persistent common atrioventricular canal type.

Hemodynamics

Measurements of pressure obtained during catheterization or operation or both disclosed closely similar systolic pressures in the right and left ventricles. In case 3, the oxygen saturation in the pulmonary artery was almost equal to that in the radial artery, which may be attributed to nearly complete mixing of systemic venous and left ventricular blood in the right ventricle. The pulmonary blood flow depends on the relative levels of pulmonary and systemic vascular resistance. With a lower pulmonary resistance, the pulmonary flow will be greater than the systemic flow, as in case 3.

In the presence of both an extremely high pulmonary flow and good mixing in the right ventricle, the oxygen saturation of pulmonary arterial blood can be equal to that in the systemic arterial system, and the systemic arterial blood oxygen saturation can approach normal values. If, during cardiac catheterization, a left-to-right shunt at the ventricular level is found and the oxygen saturation in the pulmonary artery is equal to that in one of the systemic arteries, the diagnosis of a single ventricle[17, 18] or the origin of both great vessels from the right ventricle is suggested. Determination of the anatomic positions of the semilunar valves and the great vessels may help to differentiate these two conditions.

In a single ventricle without pulmonary stenosis,[17] the relative positions of the aorta and pulmonary artery frequently are reversed. The ascending aorta lies ventral and parallel to the pulmonary artery, with the aortic valve occupying a position that is ventral and cephalad to and to the left of the pulmonary valve.

When both great vessels take origin from the right ventricle, the ascending aorta lies to the right of the pulmonary artery and the two semilunar valves lie in approximately the same coronal and cross-sectional body planes.

The relationship of the great vessels to each other may be demonstrated by positioning two catheters simultaneously in the aorta and pulmonary artery, which demonstrates that the aorta is to the right of the pulmonary artery, with both lying parallel in postero-anterior as well as lateral views. This procedure also shows that the cephalocaudal levels of the aortic and pulmonic valves are similar (fig. 10*a*). In the lateral view, the catheters appear to be approximately in the same coronal body plane (fig. 10*b*).

Some cases of origin of both great vessels from the right ventricle (as well as some cases of single ventricle)[17] show poor mixing of venous and arterial blood in the ventricle. In these instances, a streaming effect apparently exists,[14] the left ventricular blood being shunted preferentially through the ventricular septal defect directly into the aorta and the right ventricular blood being directed into the pulmonary artery. When this occurs, the oxygen saturation of the pulmonary arterial blood is significantly less than that of the systemic arterial blood. Such patients present a difficult diagnostic problem at cardiac catheterization, because the data on blood oxygen saturation obtained from the cardiac chambers and great vessels resemble those in patients who have the usual type of ventricular septal defect with a large left-to-right shunt.

A clue to the correct diagnosis of common origin of the great vessels from the right ventricle can be obtained at cardiac catheterization in such patients by recognizing the unusual positions of the aorta and pulmonary arteries in relationship to each other, as well as the anatomic relationships of the semilunar valves. Demonstration of these unusual anatomic relationships can be particularly clear cut if the two-catheter technic (fig. 10) or biplanar selective angiocardiography is used.

Summary and Conclusions

Clinical, hemodynamic, and pathologico-anatomic findings were studied in eight cases in which both great vessels took origin from the right ventricle in the absence of pulmonary stenosis. In each case, a ventricular septal defect constituted the only outlet for

the left ventricle. The aortic and pulmonary valves were in approximately the same cross-sectional and coronal body planes, which contrasts to the situation in the usual ventricular septal defect, in which the aortic valve lies in a normal position, being caudal to the pulmonary valve.

The clinical features simulated those of a large ventricular septal defect associated with pulmonary hypertension. The importance of distinguishing these two anomalies is emphasized, since the surgical methods for repair are different.

The following findings aid in the differential diagnosis: (1) electrocardiography shows a manifest mean electric axis above the zero line, with the frontal-plane vectorial loop of the QRS directed in a counterclockwise direction and its main portion lying above the zero line; (2) cardiac catheterization or angiocardiography or both demonstrate that the aortic valve lies at the same cross-sectional body level as the pulmonary valve in the anteroposterior view and at the same coronal plane in the lateral view; (3) in some cases, the oxygen saturation of blood in the pulmonary artery approaches or equals that in the aorta, indicating that relatively complete mixing of pulmonary venous and systemic venous blood has occurred in the outflow tract of the right ventricle.

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Further Studies on a Theory of the Ballistocardiogram

By ABRAHAM NOORDERGRAAF, PH.D.

IN THIS THEORY of the normal human longitudinal ballistocardiogram we shall attempt to relate the record, in quantitative terms, to the events in the circulation that we believe to be its genesis.

The variables concerned here fall into three groups: those concerned with the performance of the heart as a pump; those concerned with the position and elastic properties of the vessels that contain the blood and guide its movement; those concerned with the properties of body tissues themselves that influence the transfer of forces arising within the body to its support, the ballistocardiograph. Mainly the first two groups are discussed in this paper. The fourth group, comprising the properties of the instrument, has been discussed extensively.

As the simplest approach to the problem we have taken as our starting point the movement of the body in space, when the body is free to move, with the events of the cardiac cycle. It is of interest to note that the advantages of this approach were recognized by Trotter in 1872, when he commented on Gordon's paper, the first on this subject.

Such an approach is based on a well-known principle. Figure 1 shows a striking example that is within the experience of everyone. If an object is free to move, when the internal position of its center of gravity is altered by forces arising within it, the object alters its position in space so that the position of its center of mass in space remains the same. This is why the fisherman has so much difficulty recovering his hat.

The body, placed in position in which it is free to move in space, will behave similarly. Shortly after the onset of systole, when blood is first driven headward out of the heart to distend the great vessels, the internal center of gravity of blood moves headward in the body. Later, as the pulse wave spreads peripherally, blood accumulates at a great distance from the heart in the more peripheral vessels, so that the center of gravity moves footward within the body. But if the body is free to move in space, the center of gravity of body, blood, and support does not move at all in space; it is the body that moves first footward and then headward during the cardiac cycle (fig. 1).

Such a movement has three interrelated quantities—displacement, velocity, and acceleration—and each of these can be recorded by an appropriately designed ballistocardiograph. It is our aim to calculate what each of these records would look like from data concerned with the physical properties and performance of the heart, circulation, blood vessels, and body tissues. Most of the values needed for this calculation were secured from the literature, some were determined by measurement and experiments made to secure them for this study. In a few instances values consistent with other information on the subject were assumed. From such data we have been able to calculate the theoretical ballistocardiogram from normal values of cardiac performance and tissue properties. And, finally, these theoretical ballistocardiograms have been compared with the records secured on healthy persons by the best modern instruments. Part of these results were reported previously.[1, 2]

In our previous studies[1-5] we computed from physiologic and anatomic data the effects caused by the movement of blood in the ventricles and the larger arteries of both the systemic and pulmonary trees. This accounted for a large part of the ballistocardiogram but

From the Department of Therapeutic Research, The University of Pennsylvania, Philadelphia, Pennsylvania, and the Department of Medical Physics, Physical Laboratory, University of Utrecht, Utrecht, The Netherlands.

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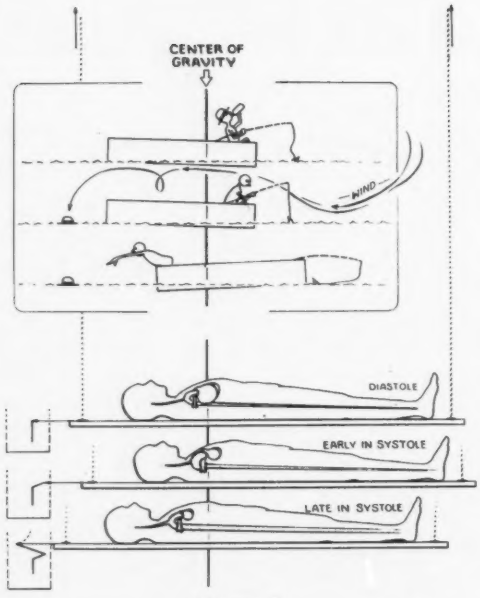

Figure 1

Top. *Diagram illustrating that the common center of gravity of fisherman and boat keeps a constant position with respect to the bottom of the lake. The boat is supposed to move freely in the horizontal plane. The initial velocity of the boat equals zero.* Bottom. *When the distribution of blood changes within the subject's body the ultra-low frequency ballistocardiograph moves in opposite direction such that the common center of gravity of subject and support remains in the same position.*

not for all of it. In the present paper our estimate of the contribution of changing amounts of blood in the pulmonary arteries to the internal movement of the center of gravity has been improved, new data permitting a more accurate estimate. And in this new study we have also calculated the contributions of the changing volume of the small arteries, of the refilling of the heart, of the contractions of the atria and, finally, of the movement of the heart wall itself. The effect of soft tissue motion is also discussed. So the studies reported in this paper present a more complete theory by covering not only the systolic and diastolic but also the presystolic waves of the ballistocardiogram.

In calculating the contribution of each of these items to the movement of the center of gravity within the body, and so to the ballistocardiogram, the same method has always been used. The change in mass at each position at every instance of the cardiac cycle is estimated for every location studied. This is multiplied by the distance of that location to an imaginary plane, perpendicular to the longitudinal axis, and passing through the heart; it is indicated by the line shown passing through the upper body in figure 1. The curves thus obtained for each location are aligned in time and the values for each instant added together to form a composite curve that represents the movement of the body's center of gravity within the body during the cardiac cycle, assuming that no deformation occurs in the transfer from circulatory system to body frame. This theoretical curve is to be directly compared with the record of the ultra-low frequency ballistocardiograph when displacement is recorded; its first derivative is to be compared with the record of the same instrument when velocity is recorded; its second derivative is to be compared with "force" ballistocardiograms, i.e., the ultra-low frequency record when acceleration is recorded, and the high-frequency ballistocardiogram when displacement is recorded.

The newer contributions to the theory are now taken up in order.

Contribution of the Lesser Circulation

According to the anatomic data on which we previously relied,[6] the relation between the thickness of the wall and the internal radius of the arteries belonging to the lesser circulation is the same as that found in the systemic circulation. Since there was some doubt about the validity of this statement, we made some measurements on the wall thickness of the pulmonary artery and of the ascending aorta in human cadavers. The results suggested that if the thickness of the wall of the pulmonary artery is assumed to equal around 55 per cent of the thickness of the wall in a corresponding location in the aorta, more accurate results would be secured.

Because of the lack of data on the elasticity of the pulmonary arteries, in a previous

Table 1

Survey of Anatomic and Physiologic Data Used for Calculating Changing Blood Volume in Pulmonary Arteries during Cardiac Cycle

No. of artery	R (cm.)	t' (cm.)	r (=R−t') (cm.)	a (=r/t')	S (cm.²)	dS/dp (10^{-6} Gm.$^{-1}$ cm.^{3} sec.^{2})	Length (cm.)
28	1.40	0.080	1.32	16.5	5.47	74	1.9
29A	0.95	0.059	0.89	15.1	2.50	31	6.2
29B	1.05	0.063	0.99	15.7	3.10	40	10

R and r are the external and internal radius, respectively; S stands for the internal cross-sectional area; and p for the pressure. The Poisson ratio of the arterial wall material is assumed to be 0.5. The numbers of the arteries are the same as in reference 4.

publication we applied to the pulmonary arteries the same modulus of elasticity E (Young's modulus) that we had used for the systemic tree, namely $E = 4.0(\times 10^6$ Gm. cm.$^{-1}$ sec.$^{-2}$). Recently we have obtained some new data from direct measurements of the elasticity of the pulmonary vessels of cadavers, which made us conclude that the value we had previously used was too high. From Lawton's[7, 8] measurements on excised strips of the human systemic arteries, in which he applied a stress that was a periodical function of time, we calculated the modulus of elasticity. The average value for E turned out to be 3.8, confirming our earlier choice excellently. But from his measurements on the pulmonary artery of a monkey we calculated E = 2.0, half the value we used. Moreover, Lawton performed some measurements on the pulmonary and the systemic arteries of one dog, which resulted in values of 4.5 and 6.0, respectively. The latter value is much higher than the values he secured previously from measurements on several dogs, which show an average of 4.8. But we may conclude that the pulmonary artery has a modulus of elasticity considerably smaller than that of the systemic arteries. In this dog the ratio was 1:13.

Besides these recent data we found that static measurements of this modulus had been made by Hochrein several years ago. He measured the elasticity of excised segments of human arteries[9] as well as that of excised strips,[10] but most of his measurements were made with internal pressures larger than those found during life. Hochrein's results show extremely high values for the modulus; the ratio between the moduli for the pulmonary artery and the aorta at normal blood pressures may roughly be approximated as 1:6 from one paper[9] and 1:3 from another.[10]

Finally we found in the literature in vivo measurements of the pulse wave velocity in the pulmonary arteries of dogs giving an average value of 3.8 10^2 cm. sec.$^{-1}$.[11, 12] These data did not include the radius or wall thickness of the arteries tested. By assuming anatomic values that were in the normal range, the modulus of elasticity can be calculated from this average pulse wave velocity; the values found ranged from 1.5 to 2.3.

From all these data we concluded that a reasonable assumption for the modulus of elasticity of the human pulmonary arteries would be E = 2.0 10^6 Gm. cm.$^{-1}$ sec.$^{-2}$, half the value we assumed previously. The other data used in our new setup for the calculations are compiled in table 1. The general method of making such estimates has been described before.[1] In this and previous calculations left and right ventricular ejection is assumed to start (at instant 0) and to stop (275 milliseconds later) simultaneously. It may be noted that asynchrony could cause a notched I peak in the acceleration (force) curve (fig. 4) as has been suggested before.[13, 14]

The result of this computation, i.e., the contribution of blood movement in the right ventricle and the large pulmonary arteries are plotted in figures 2 to 4. The result obtained

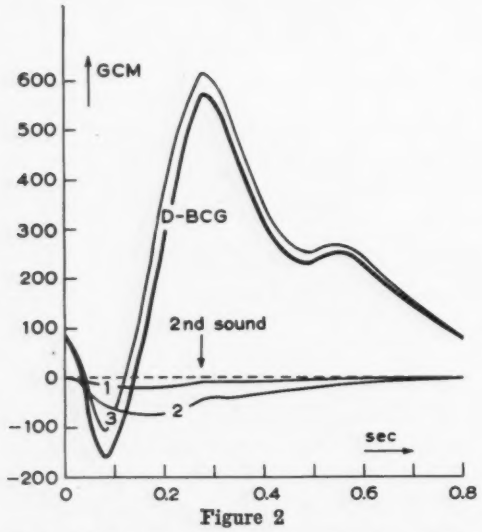

Figure 2

The contribution of the right ventricle and the pulmonary arteries to the ultra-low frequency displacement ballistocardiogram as calculated previously (1) and as revised (2). The contribution of left ventricle and systemic arteries as calculated previously (3). The heavy black line gives the total predicted displacement ballistocardiogram due to left and right ventricular and arterial activity (sum of 2 and 3).

previously is marked 1, that with the improved data is marked 2, and is significantly larger, as could be expected from the direction of the change in the numerical values. The left ventricular and systemic contribution is shown separately in figure 2 (marked 3). The heavy black line gives the total predicted movement due to left and right ventricular and arterial activity.[2] The effect of movement of blood in systemic vessels is conspicuously larger than that of movement in the lesser circulatory system.

Contribution of Movement of Blood in the Small Systemic Arteries

In the preceding study of blood movement in pulmonary vessels[1] and in published papers on that in systemic vessels[1, 2] the contribution to the ballistocardiogram of pulsatile changes in blood content of the arteries with an internal diameter smaller than 0.22 cm. was not taken into account. It is evident that the rhythmic change in blood content of any small artery with the arrival and departure of the pulse wave must be negligible in comparison to that occurring in a large artery. Since the small arteries so outnumber the large arteries, their total effect is not necessarily close to zero. So an attempt was made to get an idea of the contribution to the motion of the internal center of gravity due to the mass of blood pulsating in the small arteries. Because of lack of reliable data in man the result of the computation must inevitably be a first-order approximation only.

The line of thought that was presented earlier[1, 4] will also be applied here. Just before the arrival of the pulse there is a certain amount of blood within each segment of artery. With the increase of pressure that marks the pulse the volume of blood contained in each segment increases. The volume of blood above the diastolic volume level, $\triangle V$ at any instant can be estimated from the increase in the internal pressure above the diastolic pressure level at that instant, $\triangle p$ by the following equation:

$$\triangle V = \frac{3V(a+1)^2}{E(2a+1)}\triangle p \qquad (1)$$

V is the volume of the considered artery, E the modulus of elasticity (Young's modulus) of its wall material, and a the ratio between the internal radius and the thickness of the wall.

Since it is impossible to carry out this calculation for each small artery in the body, some means must be found to deal with them in groups. It should be kept in mind, however, that the pulse wave does not arrive in all parts of the arterial bed at the same time; e.g., it arrives at the coronaries before it reaches the arteries of the calf. In order to take into account the time of arrival the small arteries were divided into groups according to their general location in the human body. The average delay of the pulse in each region of the body had been calculated previously,[1] and the same values were used in this study.

The form and amplitude of the pressure wave in the small arteries of each region were assumed to be equal to those in the larger arteries[4] supplying that special section. Since

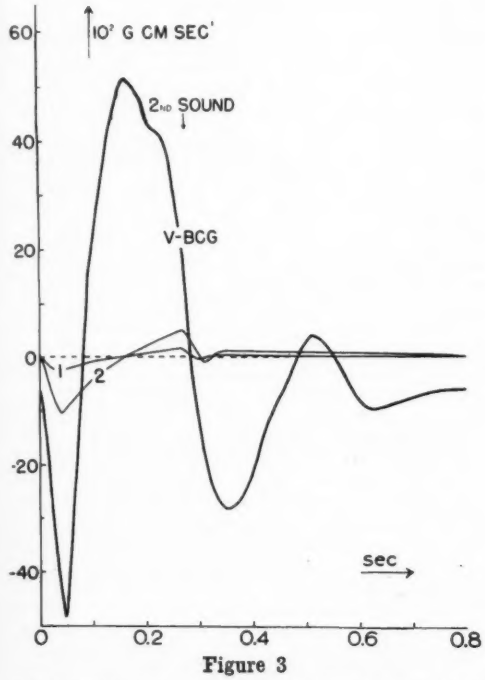

Figure 3

The contribution of the right ventricle and the pulmonary arteries to the ultra-low frequency velocity ballistocardiogram as calculated previously (1) and revised (2). The heavy line shows the total predicted velocity ballistocardiogram due to left and right ventricular and arterial activity.

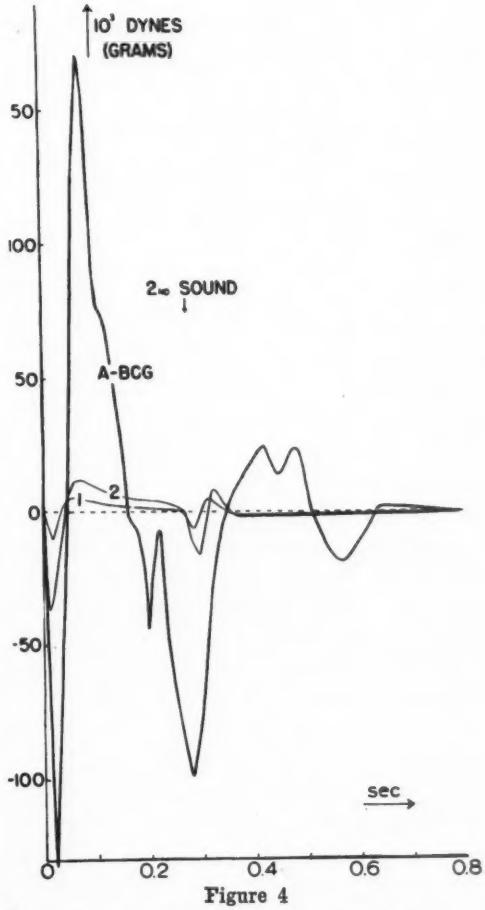

Figure 4

Same as figure 3 for the acceleration ballistocardiogram.

the effective length of the small arteries has been reported to be very small (Green[15]), we did not correct for the time required for the pulse to traverse these vessels.

The many small arteries comprised in this estimation have of course a whole range of values of internal radii and wall thicknesses, the ratio of which (a) appears in the formula given above. A study of the data compiled from the literature by Horeman[16] indicates that three is a reasonable average value for this ratio in the smaller arteries. The value of E was assumed to be the same as for the large systemic arteries, namely $E = 4.10^6$ Gm. cm.$^{-1}$ sec.$^{-2}$, no other data being available.

The remaining values needed to solve equation (1) are those of the diastolic volumes V for the small arteries of the different sections of the body. Green[15] gives data about the distribution of blood in a 13-Kg. dog arranged according to the order of the branches. He estimates the volume of blood contained by the secondary branches up to the terminal branches to be 4 per cent of the total blood volume. Because of lack of similar data concerning the human arteries we assumed that the smaller arteries of man would contain the same percentage of the total blood volume as they do in the dog, so in our computations V equals about 200 cm.^{3}. But what we actually needed was the value of V for the different sections separately. To approximate these amounts the distribution of the 200 cm.^{3} of blood over the various regions of the body was

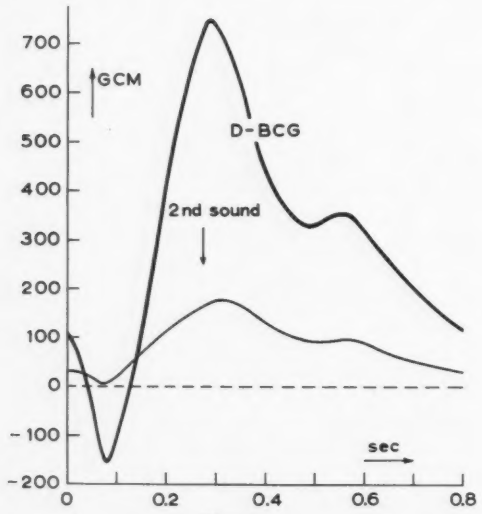

Figure 5

The light line depicts the calculated contribution of the small arteries to the displacement ballistocardiogram. The heavy line represents the calculated new total displacement ballistocardiogram, which is the sum of that obtained after the data on the pulmonary arteries were revised and of the contribution of the small systemic arteries.

assumed to be proportional to the blood flow through those regions. Data are available concerning these flows. Table 2 lists the values (and thus the proportions) used and the sources from which they were taken. Slightly smoothed-out plots of the results are displayed as light lines in figures 5 to 7. The heavy lines depict the new total estimate, which equals the sum of the predicted total curves given in figures 2 to 4, and of the values plotted as light lines in figures 5 to 7. The contribution of the changing volume of blood in the smaller arteries turns out to be much smaller than that of the large arteries, as was expected. But it amounts to roughly 20 per cent of the total effect on the ballistocardiogram.

The anatomic arrangement of the lobes of the lungs close around the heart suggests that the contribution of the small pulmonary vessels will be so much smaller than that of the corresponding systemic arteries that no estimate was attempted.

Table 2

Approximation of the Distribution of Blood Volume at the Diastolic Pressure over the Various Regions of the Human Body

Regions	Flow (cm.³/min.)	Diast. blood vol. in regions (cm.³)	Average time delay in arrival of pulse wave (m. sec.)
Heart muscle	250[17, 28]	10	0
Head	750[17, 28]	30	40
Intercostals	150	6	25
Hepatic-portal System	1500[17, 28]	60	65
Renals	1250[17]	50	65
Legs	850[17]	34	170
Arms	250[18]	10	110
Total	5000	200	

The small arterial vessels are subdivided in regions as listed in the first column. The flow through these regions and their assumed diastolic blood volume are given in columns two and three, and the average time delay before the arrival of the pulse wave after the opening of the aortic valves (reference 1) is summed up in the last column.

Contribution of Movement of Blood During Cardiac Filling and Atrial Contraction and of Movement of the Heart Itself

From the time relations it seems obvious that the movement of blood in the arterial trees is not responsible for anything that occurs in the ballistocardiogram just before the first great downstroke, the H-I segment in the force record. Therefore one should look into the events occurring on the venous side, the changes in atrial and ventricular volume during filling, the effect of atrial contraction and the movement of the heart itself, for an explanation of the initial movements in the ballistocardiogram.

A large quantity of information has been gathered about the mechanical activity of the human and mammalian heart from volume and pressure curves, phonocardiograms, electrokymograms, and densigrams,[17, 18] together with curves displaying the electrical activity. The introduction of new direct methods of measurement by Rushmer et al.[19] has recently provided another source of information concerning cardiac contraction. But not much has been done since Wiggers[20] to correlate the various cardiac events, which can be measured

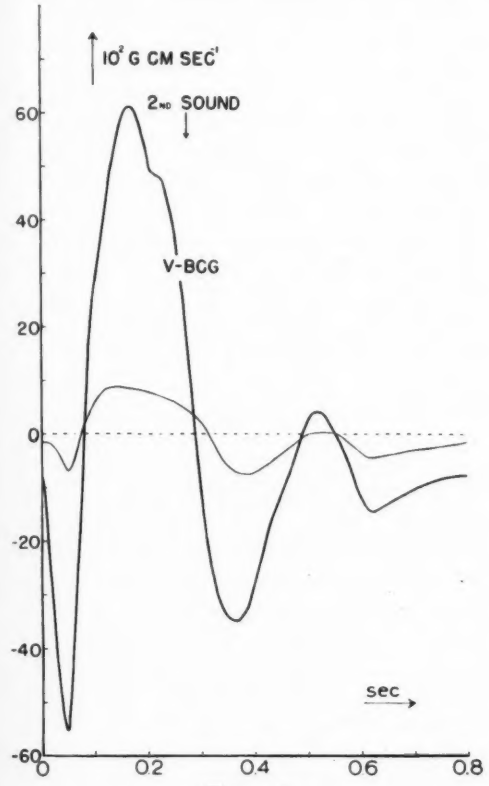

Figure 6

Same as figure 5 for the velocity ballistocardiogram.

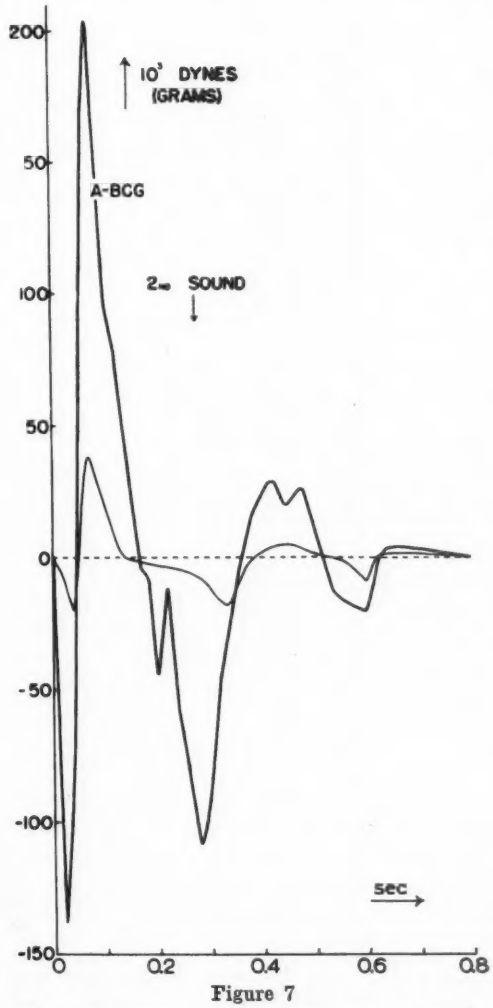

Figure 7

Same as figure 5 for the acceleration ballistocardiogram.

quantitatively, in order to thus obtain a more general picture of the normal human heart's behavior.

Nylin[21] estimated that the residual blood volume in the heart of a recumbent subject averages around 350 cm.³. We assumed that 150 cm.³ is stored in each ventricle and 25 cm.³ in each atrium. If we assume a stroke volume of 75 cm.³, this estimate together with Wiggers' curve of the change in ventricular volume gives the value of the ventricular blood volume V_{ventr} at each instant of time. We then assumed that the ventricle has a spherical shape during ejection. The internal radius of the ventricle r_{ventr} during systole with regard to time can then be computed readily from $V_{ventr} = \frac{4}{3}\pi r^3_{ventr}$. This gives us the distance between the center of gravity of the ventricle and the annulus fibrosus during ejection. Since it is very likely, however, that the ventricle assumes a less globular form during diastole, this distance cannot be determined from the ventricular volume only. In order to obtain an approximate value we used in addition the mean ventricular electrokymogram, Rushmer's[19] direct measurements of the ventricle's size and Chaillet's[22] observations on the motion of the mitral valves. We thus obtained a complete time course of the distance

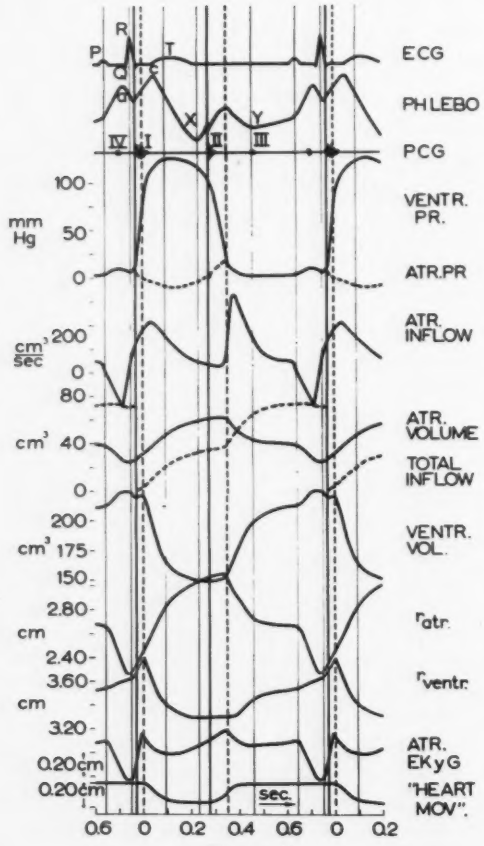

Figure 8

Composite drawing of electrocardiogram, venous pressure, phonocardiogram, left ventricular and atrial pressure, left atrial and ventricular volume, computed radius of the atrium, (r_{atr}), *computed distance between the center of gravity of the left ventricle to the annulus fibrosus* (r_{ventr}), *computed flow into the left atrium* (atr. inflow), *computed total volume flown into the atrium* (total inflow), *atrial electrokymogram, and the computed displacement of the center of gravity of the left ventricle ("heart mov."). The fully drawn heavy vertical lines and the broken ones indicate valve closures and openings respectively. The instant zero is chosen as the onset of left and right ventricular ejection.*

between the center of gravity of the ventricle and the annulus fibrosus, which is given as "r_{ventr}" in figure 8.

We were unable to find data on the change in atrial volume with respect to time during the cardiac cycle.But we can get a rough estimate of it in the following manner. The changes in size of both ventricle and atrium together with the motion of the center of gravity of the ventricle inside the thorax determine the movement of the atrial border seen in the atrial electrokymogram, the form of which is well known. We cannot, however, find both quantities from one curve, since we are dealing with a problem of two unknowns obeying one equation: The difficulty lies in distinguishing movement of the atrial border due to contraction and relaxation of the atrium from that due to movement of the heart as a whole. Once the aortic and pulmonic valves have opened the volume of each ventricle diminishes, first rapidly and then slowly. What point of the ventricle may be considered to remain stationary during the process of ejection is a question about which opinions have clashed for centuries. By some the annulus fibrosus, by others the apex has been considered to be fixed in position. Evidence presented by Brecher[23] both from previous investigations and from his own research supports strongly the conception that the atrioventricular junction moves footward during ejection, thus enlarging the atria. Altmann,[24] in describing the genesis of the venous pulse, interprets the so-called venous collapse (X-valley) by descent of the atrioventricular junction. Observations of movements in opposite directions of base and apex in cases of calcification in the base are described in the same monograph; Altmann reports excursions up to 3 cm. Also, Wolferth and Margolies[25] present quantitative proof that the left heart valve area moves footward, while the apex moves headward during contraction with total excursions of 4.5 and 13 mm., respectively; the outer border of the left ventricle was observed to move first outward and then inward, with a total excursion of 4 mm. Sundberg[26] calculated that 85 per cent of the decrease in ventricular volume can be accounted for by the movement of the base toward the apex. The discordant elements in these observations are doubtless to be attributed to abnormal cardiac movement, as many

of the hearts studied were clearly abnormal.

Searching for what unity there was in these diverse data, we assumed, as an average, that when the normal ventricle contracts the displacement of the base is twice as great as that of the apex. By means of such an assumption one can estimate the motion of the center of gravity quantitatively and so of the heart as a whole. Knowing this we then can determine the change in radius of the atrium from data secured by the electrokymogram. The residual volume being known, the radius and the volume of the atrium can also be calculated (fig. 8).

The change in volume of the atrium plus the uptake of the ventricle determines the venous return, so that the total uptake from the veins, i.e., the inflow into the heart, can be readily calculated. These results are also plotted in figure 8 as "total inflow" and "atrial inflow." This calculated atrial inflow curve can be compared with the few experimental data available. Brecher[23] has reported measurements made by a bristle flow-meter inserted into the vena cava in closed-chest experiments in dogs. The tracings Brecher obtained experimentally show one small negative and two high positive peaks in about the same phase of the cardiac cycle as in our computed curve. Brecher also found the second positive peak occurring during the ventricle's rapid filling phase to be higher than the first, as in our results. Müller and Shillingford[27] published a similar tracing taken on a normal subject. This curve shows the same general form as in our results except that the second positive peak is lower than the first.

The aspects of cardiac performance that we have just computed can be compared with well-known changes occurring during the cardiac cycle in figure 8. The vertical lines indicate the transitions of the various phases from one to another during the heart cycle, a method of showing time relationships derived from Wiggers.[28] The electrocardiogram, phonocardiogram, atrial and ventricular pressures, and change in ventricular volume were drawn in according to Wiggers' data.[20] An

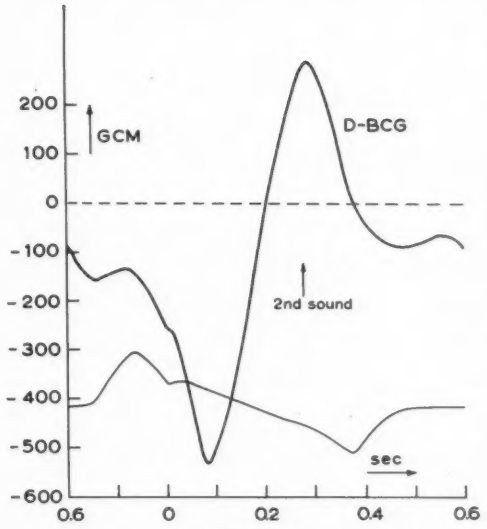

Figure 9

The light line is a plot of the calculated contribution of the filling and emptying of the heart and of its motion to the displacement ballistocardiogram. The heavy line represents the calculated new total displacement ballistocardiogram, which is the sum of that obtained after the contribution of the small arteries was taken into account and of the contribution of the filling, emptying, and motion of the heart.

average venous pulse was derived from curves presented by Wiggers,[20] Molhuyzen,[29] and Altmann.[24]

The time relations thus established, we are now in a position to compute the effect on the ballistocardiogram of atrial filling and contraction and of the movement of the heart itself. This was estimated as follows:

The contribution of an atrium equals its mass of blood ρV_{atr}, ρ being the density of the blood and V_{atr} the blood volume contained in that atrium, augmented with m_{mu} the mass of the muscle layer surrounding the blood and multiplied by the distance between the center of gravity of the atrium and reference plane $-(r_{ventr} + \frac{3}{8} r_{atr}) + p$. The factor $\frac{3}{8}$ before r_{atr} is added because the atrium is considered to be a hemisphere. The minus sign is added because of the headward position of the atrium with respect to the reference plane. The

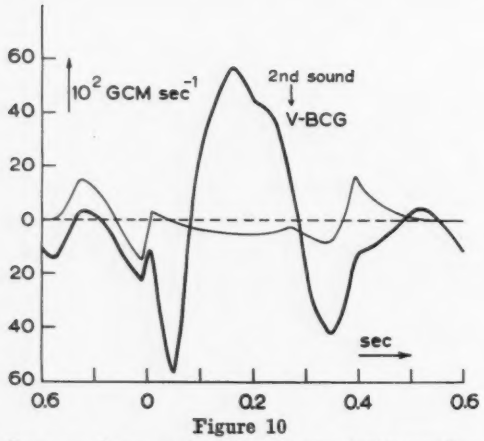

Figure 10

Same as figure 9 for the velocity ballistocardiogram.

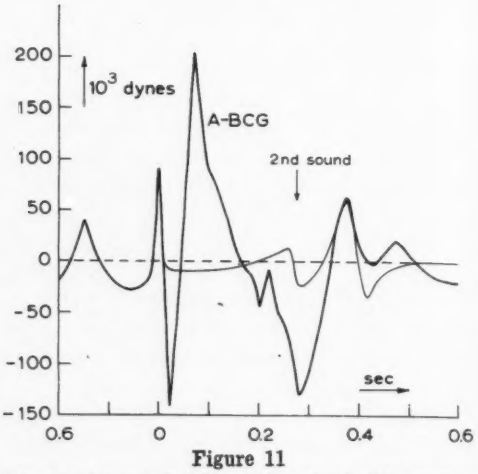

Figure 11

Same as figure 9 for the acceleration ballistocardiogram.

quantity p is the displacement of the ventricle's center of gravity caused by its special mode of contraction. Thus this contribution equals:

$$(\rho V_{atr} + m_{mu.atr})\,(-r_{ventr} - \frac{3}{8}\,r_{atr} + p) \qquad (2)$$

Since the center of gravity of each ventricle moves with respect to the reference plane we find another contribution in the same way:

$$(\rho V_{ventr} + m_{mu.ventr})\,p \qquad (3)$$

In the calculation of the total contribution to the ballistocardiogram we have multiplied the sum of products (2) and (3) in the first place by a factor 2 to take care of left and right heart sides, which are thus assumed to behave identically except for their internal pressures, and, in the second place, since the heart's longitudinal axis forms an angle of about 45 degrees with the body's longitudinal axis, by another factor cos 45° = ½ $\sqrt{2}$. The total contribution reads therefore

$$\text{BCG contribution} = \Big\{ -(\rho V_{atr} + m_{mu.atr})\,(r_{ventr} + \frac{3}{8} r_{atr}) + p\,(\rho V_{ventr} + m_{mu.ventr} + \rho V_{atr} + m_{mu.atr}) \Big\} 2.\tfrac{1}{2}.\sqrt{2} \qquad (4)$$

The mean masses of the muscle layer of an atrium and of a ventricle are taken as 25 and 140 Gm., respectively, in accordance with Vierordt's[6] data.

Figure 9 shows the calculated contribution to the ballistocardiogram of the filling and emptying of the heart and its motion as a light line. The heavy line represents the calculated total displacement curve, the sum of all the contributions studied. The calculated results for velocity and acceleration curves are given in figures 10 and 11. Figure 12 shows our final results together with average experimental tracings reported by Scarborough et al.[30] and by Rappaport.[31]

Discussion

Figure 12 shows the quite surprising correspondence between the calculated ballistocardiogram and records secured experimentally by the ultra-low frequency ballistocardiograph. Agreement between the direction and the quantitative magnitude of the waves and their relations to one another is as good as one could possibly hope for.

The most conspicuous deviation is in the timing. Thus, in Scarborough's[30] data the second sound is synchronous with the tip of the L wave of the ultra-low frequency "force" ballistocardiogram; in the theoretical ballistocardiogram the second sound occurs 50 milliseconds later. The reason for these small differences may well be caused by a slightly wrong assumption of the value of the elastic properties of the arterial wall material, i.e., in the value of Young's modulus of elasticity.

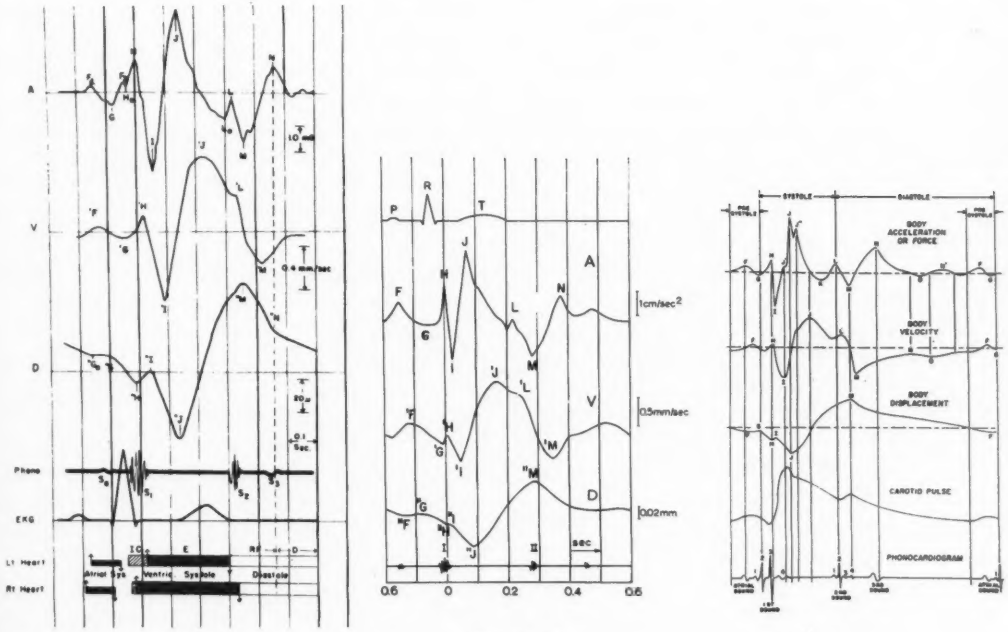

Figure 12

Left. *Reproduction of average normal experimental ultra-low frequency displacement, velocity, and acceleration ballistocardiograms as published by Scarborough et al.[30] (Am. J. Cardiol. 2: 613, 1958. Reproduced with permission of the authors and the publisher).* Right. *Reproduction of average normal experimental ultra-low frequency ballistocardiograms as published by Rappaport[31] (Mod. Concepts Cardiovas. Dis. 24: 277, 1955. Reproduced with the kind permission of Mrs. Rappaport and the publisher).* Middle. *Composite drawing of the predicted ultra-low frequency displacement, velocity, and acceleration ballistocardiograms compiled from figures 9 to 11. Records of other cardiac phenomena are given for easy time reference.*

The theoretical study throws light on the genesis of the individual waves of the ballistocardiogram. The I and J waves are caused principally by movement of blood in the great arteries of the systemic circulation; the contribution of blood in the pulmonary system is much smaller. Although the presented improvements in the computation of the pulmonary effect have increased the estimate it is still somewhat lower than the values secured by Starr in experiments on cadavers.[32] One should also note that, although the influence assigned to the pulmonary circulation is small, if blood movement in this circulation becomes asynchronous with that in the greater circulation, the forces developed in the pulmonary circulation would be sufficient to cause deep notching in the force ballistocardiogram, as is frequently observed in ultra-low frequency records.

Movement of blood in the small arteries plays a small role in the ballistocardiogram, but is responsible for some 20 per cent of the total effect, which is certainly not negligible.

In discussing the origin of individual waves one must remember that a number of events act simultaneously throughout the cardiac cycle and that a wave tip merely means that the sum of several events is maximal or minimal. Therefore a tip or inflection of the record can, in general, not be attributed to a single physiologic occurrence, which can be done fairly well in the electrocardiogram, although one event may be mainly responsible.

One must recall that a small change of blood distribution in the legs, because of the greater distance from the body's center of gravity, is very effective in altering the position of the center of gravity within the body, and thus altering the ballistocardiogram. The theoretical study supports the generally accepted views of the genesis of the I and J waves of the force record, but it has given new understanding to the waves of the terminal complex L, M, and N. Though these occur in diastole they are not to be attributed solely to cardiac filling but also to the changes in blood distributions as the descending limb of the pulse wave reaches the peripheral vessels.

The physiologic origin of the presystolic waves of the ballistocardiogram has been more uncertain and more debated than any other part of the record. The calculations suggest that, in the ultra-low frequency displacement record the "G wave is chiefly due to the shift of blood from atria to ventricles accompanying atrial contraction. In the initial part of the "H and "J waves, the ejection of blood headward and the displacement of the heart footward compete, bringing about the "I wave, which is better seen in experimental tracings than in our calculated curves. In the force tracing the GH upstroke precedes ejection and is mainly due to isometric contraction of the ventricles. Ejection begins at the tip of the H wave.

More details can easily be obtained from a comparison of figure 8, depicting the hemodynamic events, and figures 9 to 12, in which the calculated results are plotted.

While the normal ballistocardiogram is thus accounted for theoretically in quantitative terms, we must discuss several other possible effects, which, though probably having only a small effect on normal records, might under pathologic conditions play a considerable role in the ballistocardiogram.

A changing quantity of blood in the central veins would make some contribution to the ballistocardiogram. We could not, however, find sufficient data on which an estimate of the magnitude of this effect could be based. Certainly effects on the body's center of gravity due to changes of blood volume in the superior and inferior venae cavae would tend to cancel each other out, and the central location of the great veins would cause changes of their blood volume to have small influence on the ballistocardiogram. But if the great veins were congested, such effects might be larger.

When an artery changes its volume, surrounding tissue of about the same density as blood must move. It is this movement that is finally transferred to the skin. For reasons of symmetry the effect of this tissue movement on the ballistocardiogram is probably negligible. On the other hand, when the heart changes its volume or its position, or both, lung tissue with a much smaller density is caused to move. This makes the contribution to the ballistocardiogram as calculated in this paper give an estimate that will be somewhat too high.

In this paper it is assumed that there is no deformation in the transmission from the cardiovascular system to the body frame, an assumption that is not likely to be a suitable first order approximation for the higher frequency components of the force ballistocardiogram. This transmission acts as a low-pass filter.[33]

Conclusion

The greater part of the normal ultra-low frequency ballistocardiogram, when displacement, velocity, and acceleration are recorded, can be accounted for quantitatively by known hemodynamic events. Although several assumptions have had to be made in the course of the computations, the agreement between the computed curves and those obtained experimentally on healthy subjects appears to be as close as one could possibly expect, except for some difference in timing.

Acknowledgment

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Physical Aspects of the "Direct" Recording of Body Displacement, Velocity, and Acceleration by Shin-Bar Ballistocardiographs

By ABRAHAM NOORDERGRAAF, PH.D.

THE APPLICATION of physical principles to problems inherent in taking and recording ballistocardiograms has resulted, not only in greater understanding of the genesis of the record, but also in several important advances in other directions. Thus, under the impact of this analysis a new type of instrument, the ultra-low frequency ballistocardiograph, has been reintroduced and the older high-frequency instrument has been much improved.

A similar criticism, based on physical principles, has not as yet been applied extensively to some of the simpler and more popular methods of ballistocardiography; that is the aim of this paper. It can always be objected that the physical formulae used in such studies were derived either from theory, or from experiments with objects such as steel springs and oil damping, which bear little obvious resemblance to the complicated physical conditions that exist in the body where a large number of masses, some small, some large in size, are held together by bindings whose properties vary. The answer to this objection is two-fold. First the larger movements of the body studied, such as its movement as a whole on its supports, do conform closely to expectations from physical theory; and, second, the knowledge gained from calculations based on physical theory has resulted in improved methods and technics. So we have not hesitated to proceed with the calculations reported here in the expectation that they would lead to both greater understanding of the errors inherent in the simple methods and perhaps to technical improvements in the simple methods themselves.

In Dock's original method the body rested supine on a fixed surface such as a rigid table or floor. Driven by forces arising within it, the body moves back and forth on the rigid support, a motion permitted by the elastic properties of the body tissues; the ballistocardiogram is the record of this movement. The theoretical problem is, do the properties of the tissues distort the record of the forces? The practical problem is, how can a doctor who finds that the record of one person differs from that of another, be sure that the recorded difference is due to a true difference in the internal forces, and not to a difference in properties of body tissues that have nothing whatever to do with the performance of the heart? This study aims to seek an answer to these two questions.

During the first years after Dock's introduction of the shin-bar method it was customary to record either the body's displacement on the rigid surface or a mixture of displacement and velocity, which was called the "diagnostic" tracing. Later several investigators became interested in the body's velocity and acceleration (first and second time derivative of the displacement curve, respectively), as well as in displacement itself. At present some investigators are recording all three aspects of the subject's motion and others have decided to secure only one or two of the three aspects.[1-11]

By recording two or three aspects of the subject's motion one obviously gains additional easily accessible information about the

From the Department of Therapeutic Research, University of Pennsylvania, Philadelphia, Pennsylvania.

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Table 1

Survey of the Used Numerical Data

	Subject mass (Kg.)	Mass of BCG (Kg.)	Natural frequency of subject vs. support when made immovable (cps)	Natural frequency loaded BCG vs. surroundings (cps)	Fraction of critical damping of subject vs. support	Fraction of critical damping of BCG vs. surroundings
Direct body BCG	74	—	3.3	inf.	24%	—
Ultra-low frequency BCG	74	3.3	4.7	0.3	23%	40%

performance of the heart and by means of modern electronic apparatus this information is easily secured. And it has been the hope that records of velocity and acceleration, by emphasizing certain aspects of the body movement, might emphasize those aspects of the record that are of especial clinical importance.

The accuracy with which the body's displacement is recorded by the shin-bar technics is easily determined by experiment. For example, records secured by the Dock method can be compared with those obtained by modern ultra-low frequency tables. Very little information, however, has been presented concerning the accuracy of the shin-bar velocity and acceleration tracing. In this study we have employed the technics of physics to look a little more closely at the displacement, velocity, and acceleration tracings secured from light bars firmly bound to the shins, at their mutual relationships and their interpretation.

Methods

To understand the relation of the recorded shin-bar curve to the forces that produced it one needs to know the physical properties of the system concerned, and those related to the properties of the body have been calculated from available data for a subject lying on a rigid surface. In this calculation we have assumed that the usual Dock technic has been employed and that no steps had been taken to resist the body's movement on the rigid surface. We have also assumed that the body moves as a single mass. The numerical values for the various constants that determine the properties of the system schematized in this manner have been taken from experimental results published previously.[12-14] In these experiments healthy subjects lay supine on a rigid surface. The body was pushed headward (or footward) and, when suddenly released, went into a short series of vibrations of diminishing amplitude. From a record of these vibrations the frequency and damping were estimated. By this means an average value for the body's resonance frequency of 3.6 cps. and a damping averaging 24 per cent of the critical value was found (table 1).

It has been demonstrated that the shin-bar displacement tracing of a body whose movement is so resisted represents the internal forces originating the subject's movement or, what is proportional to it, the internal acceleration ($\ddot{x}_c$) of the center of gravity (c.o.g.), which is the second derivative of its internal displacement. To what extent such shin-bar displacement (x_s) curves will approximate this quantity may be seen from the amplitude and phase characteristics calculated from the data in table 1 and plotted in figure 1A.

The relation of the three shin-bar curves of displacement, velocity ($\dot{x}_s$), and acceleration ($\ddot{x}_s$) to one another and to the internal forces that originate them can be described in two ways that are mathematically equivalent.

Since the shin-bar velocity and acceleration curves are the first and second time derivative of the shin-bar displacement tracing, respectively, they may be regarded as depicting the first and second derivative of the internal forces playing on the body or as depicting the third ($\dddot{x}_c$) and fourth ($\ddddot{x}_c$) derivatives of the body's internal displacement of the c.o.g. It can be proved mathematically that the amplitude and phase characteristics holding for these relationships are identical with those plotted in figure 1A.

The body's velocity and acceleration tracings can be obtained from the shin-bar displacement curve by differentiating the latter once and twice, respectively. In the second view of the relationships we shall regard these differentiators as filters that emphasize higher frequencies in relation to lower ones.

This line of reasoning starts out from the same

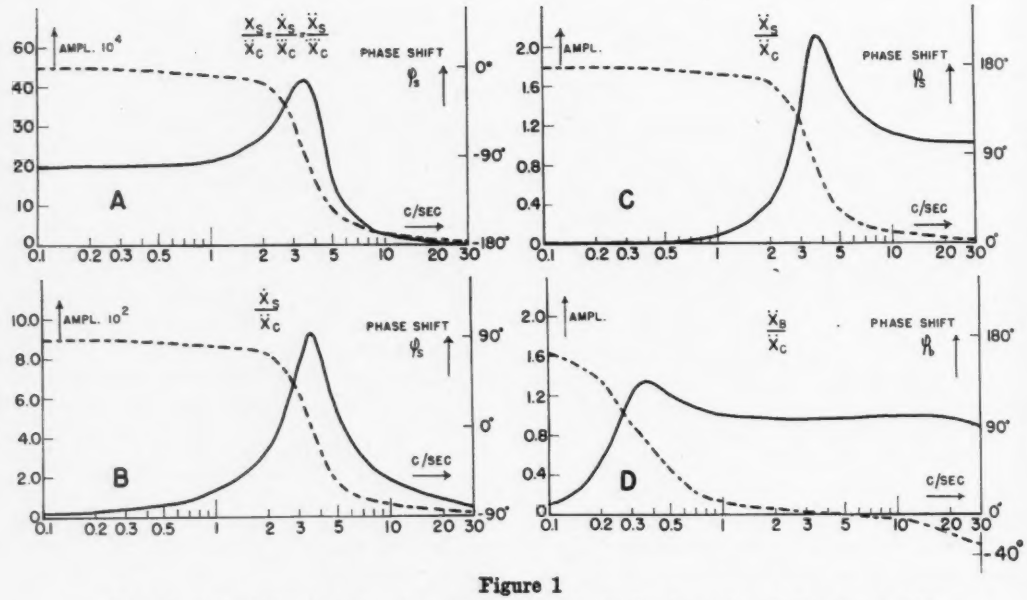

Figure 1

Characteristics indicating the change in amplitude (fully drawn) and the phase shift (broken line) for sine wave components of the subject's internal acceleration of the center of gravity ($\ddot{x}_c$) when: A *shin-bar displacement* (x_s), B *shin-bar velocity* ($\dot{x}_s$) *and* C *shin-bar acceleration* ($\ddot{x}_s$) *are recorded.* D. *For comparison the same characteristics for an ultra-low frequency instrument when the acceleration of the bed* ($\ddot{x}_b$) *is recorded.*

place as that given above, viz., the direct body displacement record is regarded as representing the internal forces. But we can also regard the body's velocity record as another representation of the internal forces, a record in which the forces are represented differently than in the displacement curve, because of the use of a filter (the differentiator). The same values being used for body frequency and damping that were secured in the experiments cited before, the manner in which the shin-bar velocity record represents the various frequencies of the internal forces was calculated and the results are plotted in figure 1B.

Likewise, the acceleration record may also be considered as a curve representing the internal forces, but again differently because of the fact that a second filter has been applied. The results, which indicate the distortion of the forces to be expected in the acceleration trace, are plotted in figure 1C.

Results and Discussion

Figure 1A gives the results calculated for the displacement record and it indicates that components of the internal forces with a frequency in the range of the body's resonance frequency are exaggerated in the record while higher frequency components of the internal forces are sharply attenuated. Thus an internal force component having a frequency close to 3.6 per second would produce a far larger deflection in the record than an internal force component of the same magnitude but of a frequency considerably higher than 3.6 per second. The results plotted in figure 1B show that frequency components close to the resonance frequency are strongly emphasized with respect to all other frequencies. Figure 1C shows a mirror image of figure 1A with respect to a vertical line through the resonance frequency; in this case lower frequencies are cut off sharply so internal force components of low frequency will be strongly attenuated.

Thus figures 1A, B, and C define the changes that will be induced in the record of the body's internal forces by the three methods of recording them, body displacement, velocity, and acceleration. Each method will exaggerate some components of the internal forces, and suppress others; the compo-

nents exaggerated and those suppressed differ in the three methods of recording. The amplitude characteristics show a frequency response that is not flat over the frequency range of the internal forces that produce the ballistocardiogram, while the phase shift is never small in the entire frequency range. Figure 1D is given for comparison; it shows a similar representation of the frequency responses of the ultra-low frequency ballistocardiograph currently in use in this department (table 1). The amplitude characteristic of this instrument is almost flat throughout the entire ballistocardiographic frequency range. The phase shift in the same range is negligible. This, then, is theoretically a much superior instrument. For any method giving a distorted picture of the forces, while it might conceivably emphasize aspects of clinical importance, might also suppress them.

Comparison between Theoretical and Experimental Results

In figure 2 tracings are shown secured on the same normal subject with the Arbeit displacement, velocity, and acceleration ballistocardiograph, the so-called D-V-A instrument, and with the above-mentioned ballistocardiograph of ultra-low frequency. Inspection of these curves suggests immediately that frequencies around 4 cycles per second predominate in the direct body curves while that is not the case in the ultra-low frequency tracing (bottom). Thus the experimental results confirm the expectations derived from the theoretical calculations. The direct body ballistocardiogram, as it is usually recorded, is much influenced by certain physical properties of the body that have been defined in figures 1A, B, and C.

We have thus developed a theory that accounts for differences found among the three types of shin-bar records and the ultra-low frequency record. If this theory were correct, given any shin-bar record, one should be able to compute what that subject's ultra-low frequency record would look like, and vice versa. Indeed the ability to do this would go far toward establishing the validity of the theory. Such a calculation can be carried out with

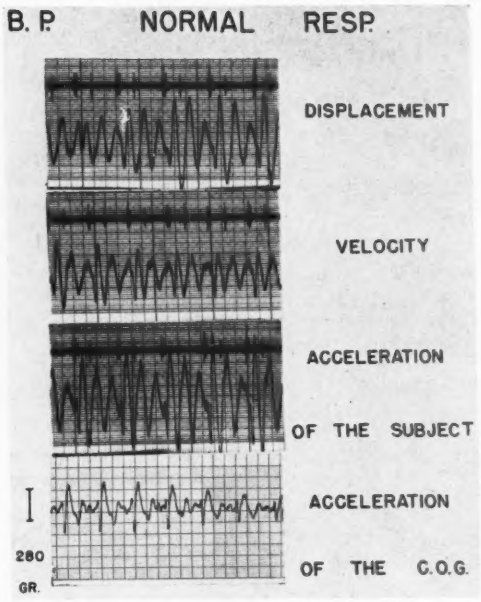

Figure 2

Direct body displacement, velocity, and acceleration tracings together with an acceleration tracing secured from an ultra-low frequency ballistocardiograph (bottom) of the same normal subject. The four ballistocardiograms were taken consecutively during rest. The direct body tracings were taken by Dr. Nahum J. Winer and are reproduced with his kind permission.

the aid of Fourier analysis; if it were to be performed by ordinary methods of computation, it would require so much time that it would be altogether impracticable to attempt it. The development of modern computing machines has, however, made such a transformation feasible. With the assistance of Mrs. Maxine L. Rockoff the data described below were prepared so that the computations could be performed by the Univac Digital Computer at the University of Pennsylvania.

A typical average force ballistocardiogram, secured on a healthy subject by the ultra-low frequency method was taken as a starting point. The complex used is the fourth from the left in the lowest curve in figure 2 and it is enlarged to make figure 3A.

By Fourier analysis this curve was developed into a series of 60 harmonics the ampli-

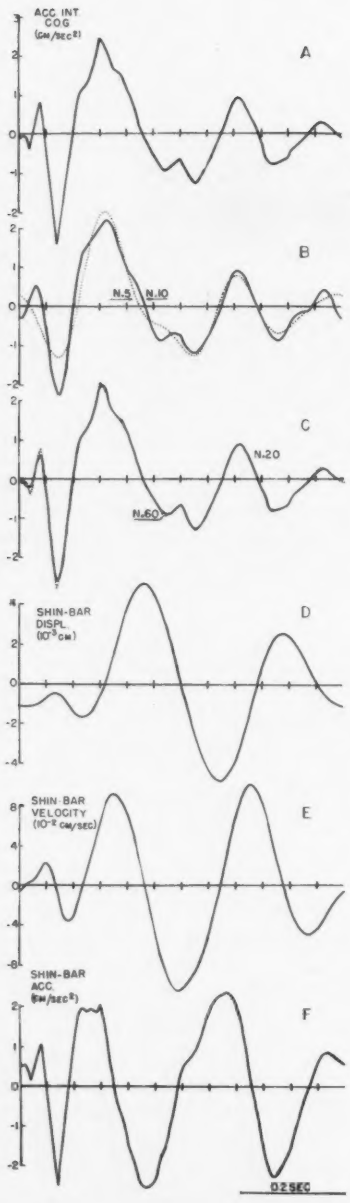

Figure 3

A. *Enlargement of the fourth complex from the left of the ultra-low frequency tracing shown in figure 2 (bottom). The amplitude is calculated from the calibration given in figure 2.* B. *Synthesis of the curve in figure 3A using the first 5 (dotted line) and first 10 terms of the Fourier series in which the experimental curve was developed.* C. *As* B *for the first 20 terms (fully drawn) and all 60 terms.* D. *The computed shin-bar displacement curve.* E. *The computed shin-bar velocity curve.* F. *The computed shin-bar acceleration curve. All curves are synchronous.*

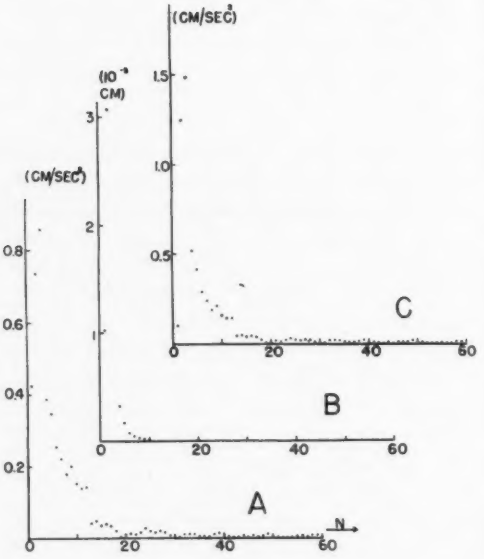

Figure 4

Amplitudes of the Fourier harmonics. A. *For the ultra-low frequency tracing shown in figure 3A.* B. *For the computed shin-bar displacement curve plotted in figure 3D.* C. *For the computed shin-bar acceleration curve shown in figure 3F.*

tudes of which are shown in figure 4A. Figure 3B shows two plots of the synthesized curves obtained by adding the first 5 and 10 harmonics; in figure 3C are plotted similar curves for the first 20 and 60 harmonics. It turns out that the sum of the first 20 harmonics approximates the experimental curves very closely. Figure 5 shows the improvement of the approximation as a function of N, the number of harmonics added together.

The ultra-low frequency curve having been thus developed into its series by Fourier analysis, we were now ready to compute what the shin-bar records of this subject would look like if our theory was correct.

Figure 3D depicts the ultra-low frequency tracing distorted according to the amplitude and phase characteristics as calculated for

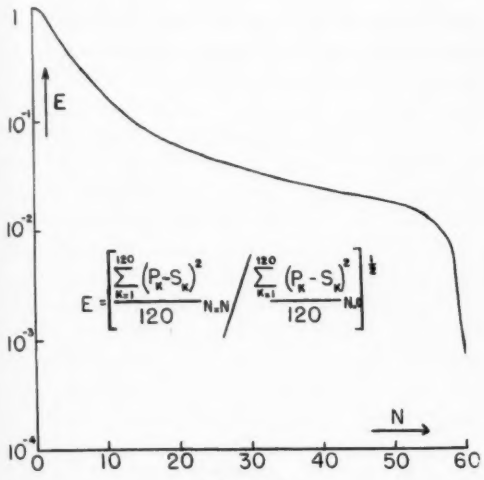

Figure 5

Normalized values of the mean difference between the 120 equidistant amplitude samples (P_k) *read from the experimental record given in figure 3A and the corresponding amplitudes* (S_k) *of the synthesized curve using the first N harmonics (N = 0, 1, ..., 60; N = 0 gives the base line).*

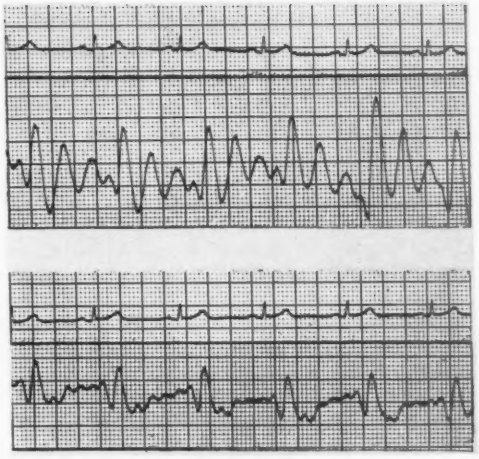

Figure 6

Simultaneous records of shin-bar displacement and electrocardiogram in the cases in which the subject is free to move on his own tissue layer (top) and his movement is resisted by the use of a non-slip pad and a footplate (bottom). (The records in this figure and in figure 2 were taken on the same subject.) The improvement of the record may be noted by comparing these tracings with the bottom record in figure 2.

the shin-bar displacement curve (fig. 1A). In order to obtain this result all 60 harmonics were changed in amplitude according to the amplitude characteristic in figure 1A (resulting in amplitudes plotted in fig. 4B) and shifted in phase according to the calculated phase shift also given in figure 1A. The sum at each instant of the thus distorted harmonics is the curve in figure 3D. This is the theoretical shin-bar displacement curve of this normal subject.

To estimate the theoretical shin-bar record when velocity is recorded, the harmonics of the ultra-low frequency curve were treated similarly by means of the theoretical data given in figure 1B. After another addition of adjusted harmonics, instant by instant, their sum (fig. 3E), is the theoretical shin-bar record, when velocity is recorded, for this subject.

By means of the theoretical data given in figure 1C the theoretical shin-bar ballistocardiogram, when acceleration is recorded, was computed in a similar manner. The resulting amplitudes are plotted in figure 4C and the resulting ballistocardiogram in figure 3F.

The theoretical shin-bar ballistocardiograms (fig. 3D, E, and F) can now be compared with the shin-bar records secured on the same subject by an Arbeit D-V-A apparatus (figs. 2 and 6, top). The resemblance is certainly very striking. Since, by means of our theory one can compute from an ultra-low frequency record the form of the three shin-bar records, the theory is on the whole satisfactory and the cause of the differences between records of the two types is clearly understood. This difference is due to the physical properties of body tissues, whose influence, minimized by the ultra-low frequency technic, plays a larger part in determining the contour of the three types of shin-bar records.

Difficulties with the Shin-Bar Method As Used at Present

It should be noted that the curves depicted by solid lines in figure 1A, B, and C show a sharp peak to the amplitude characteristic.

Also the phase shift changes rapidly where the resonance peak is located. This means that small changes in the frequency of the components, such as would be expected from changes in heart rate, will result in considerable changes in the amplitude and timing of the recorded waves. Thus a given force, delivered at one heart rate, will be recorded quite differently from the same force delivered at another heart rate.

The same difficulty holds when the actual performance of the heart and the large vessels changes, as this is liable to alter the relative importance of the various harmonics. This means that not every change in wave form and amplitude recorded by shin-bar methods can properly be attributed to changes in the heart's performance or in the cardiovascular system, although great differences of cardiac performance will undoubtedly be detected by shin-bar methods as they are used at present.

Improvement in Shin-Bar Records

This study not only indicates certain deficiencies of shin-bar methods but it also suggests means of improving these simple methods. The theory indicates that the shin-bar displacement record would be improved by tightening the body to its support. Theoretically this procedure would increase the body's resonance frequency and the characteristic given in figure 1A would shift to the right. This would result in an extension of the frequency range so that the internal forces acting on the body would be more accurately represented in the record than when the technic in common use today is employed. Thus one could predict that a shin-bar tracing, secured after tightening the subject, should be much more similar to the ultra-low frequency record (fig. 2, bottom) than is the direct-body displacement record taken by the usual technic.

The results of a simple experiment confirm this prediction. Figure 6 shows a comparison of two shin-bar records taken on the same subject; the first is a displacement record taken by the usual shin-bar technic in which the body is free to move on its support; the second was taken with the subject resting on a non-slip pad and with the feet pressed against the wall, a change in the usual technic that raised the body-table frequency from 3.6 to 5 cps. Although a very definite improvement in the shin-bar record emerges, identity of the two records was not attained. Nevertheless this simple change in technic, easily accomplished in practice, goes a long way toward closing the gap between simple shin-bar records and those taken with modern equipment. That improvement in the record would result from tightening the subject to his environment was realized by Walker et al.,[15] who sought to obtain this effect by the use of sand or putty.

The recent evaluation of filter systems and mixing circuits to correct for body resonance properties promises a considerable further improvement in the quality of the direct-body ballistocardiogram though at the cost of some loss of its original intriguing simplicity.[16-20]

Summary and Conclusions

Making use of the average values for frequency and damping of a body lying supine on a smooth rigid support, and of well-known physical principles, a theoretical study has been made of the simple shin-bar ballistocardiographic methods, when displacement, velocity, and acceleration are recorded. The resulting theory indicates that the physical properties of the body exaggerate certain aspects of the internal forces and attenuate other aspects, so that these records are distorted.

In an elaborate mathematical computation we have sought to test the correctness of our theoretical viewpoint. The form of an average complex secured on a healthy subject by a modern ultra-low frequency instrument has been taken as a starting point. Then, by means of the theory suggested, we have calculated what the shin-bar displacement, velocity, and acceleration records of that subject should look like. The result closely resembles the curves secured when these methods were actually applied to that subject, thus providing strong evidence for the correctness of our theory.

The theory also suggests that shin-bar bal-

listocardiograms would be improved by attaching the subject more tightly to his support. In a few simple experiments such tightening of the attachment has altered the shin-bar records until they approached the form found in modern ultra-low frequency records. Identity of the two types of records, however, has not yet been secured.

Acknowledgment

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Ballistocardiographic Evaluation of the Cardiovascular Aging Process

By ARTHUR J. MOSS, M.D.

CARDIOVASCULAR aging is a complex phenomenon associated with a gradual, yet progressive, deterioration in cardiovascular function.[1-3] The etiology of this deterioration in function is poorly understood, but atherosclerosis and, in particular, coronary artery disease seem to be a factor.[3] Cardiovascular aging and atherosclerosis appear to be universal phenomena, but their rate of development and the extent of myocardial involvement are variable. When there is accelerated cardiovascular aging, clinical disease develops at an unusually early age. Thus, coronary atherosclerosis is not limited to older age groups, and coronary artery disease has been demonstrated in a large number of young, healthy men aged 20 to 40.[4-7]

The clinical evaluation of the cardiovascular aging process has been difficult, for usually there are no signs or symptoms detectable until overt disease is present. The ballistocardiogram has been used for many years in the evaluation of cardiovascular function. This technic offers a unique means of studying the change in cardiovascular dynamics with age. Recently, Reeves et al.[8, 9] described an ultra-low frequency acceleration ballistocardiograph that met all theoretic considerations of biophysical design.[10-14] This ballistocardiograph was clinically adaptable, had high test-retest reliability, and revealed considerable new information about cardiovascular events. The purpose of the present study is to elucidate with the Reeves technic the changing ballistocardiographic pattern with advancing age in an overtly healthy male population, and thus to evaluate the cardiovascular aging process.

From the Cardiology Research Department, U. S. Naval School of Aviation Medicine, Pensacola, Florida.

Opinions and conclusions contained in this report are those of the author and do not necessarily reflect the views nor the endorsement of the Navy Department.

Methods and Material

Subjects

The subjects consisted of 307 overtly healthy men, aged 18 to 54, on active duty in the U.S. Navy; most were U.S. Navy pilots. The subjects were seen randomly as part of a required annual physical, and all had been screened for evidence of hypertension, rheumatic heart disease, and symptomatic cardiovascular disease. All subjects were considered to be in excellent health. The number of subjects in each of four arbitrary age groups (18 to 24, 25 to 34, 35 to 44, 45 to 54), the mean age of each group, and the average height and weight with the ranges observed are presented in table 1. On each subject a ballistocardiogram and a standard 12-lead electrocardiogram were taken.

Apparatus

The ballistocardiograph (fig. 1) was a modification[15] of the ultra-low frequency model described by Reeves et al.[8, 9] The bed platform (13 lb.) was made of honeycomb aluminum* and was suspended from a wooden frame by three 56-inch long, 3/64-inch twisted seven-strand stainless-steel cables. A hydraulic lift system raised the bed platform and disengaged it from cable support when not in use. When freely suspended by the cables, the bed was free to move in head-foot and lateral directions. A single-action joint attached between the foot of the bed and the wooden frame allowed unrestricted head-foot motion, but limited the lateral motion to the head end of the table. In the head-foot and lateral directions the suspended bed had a natural frequency of 0.42 cycle per second, with a damping factor of 0.04. The lower end of the undistorted frequency response of the bed was 0.5 cycle per second. For details on this aspect of the apparatus the analysis of Burger should be consulted.[16]

In the head-foot axis only, the motion of the bed was sensed as acceleration by an electronic accelerometer.† The accelerometer gave readings

*Honeycomb Corporation of America, Bridgeport, Connecticut.

†Northam Accelerometer, Model A-14. Northam Electronics, Inc., Altadena, California.

Table 1

Population Characteristics

Age groups	Number of subjects	Mean age (yr.)	Height (in.)		Weight (lb.)	
			Mean	Range	Mean	Range
18-24	81	21.2	69.9	66-74	165.3	130-217
25-34	56	29.4	70.6	67-75	172.7	130-247
35-44	129	39.7	70.0	66-78	173.0	142-238
45-54	41	47.7	69.5	64-75	174.2	140-215

comparable to the electrokinetic device of Elliott et al.[17] It had a flat frequency response up to 40 cycles per second, was adequately stable, and gave a satisfactory output with no phase shift. The accelerometer was attached to the under surface of the bed at the approximate theoretic heart position, and the signal was fed into a strain-gage amplifier on a Sanborn Poly-Viso direct recorder. The polarity of the accelerometer was placed so that a headward force produced an upward deflection of the recording stylus and a footward force a downward deflection. The lateral motion of the bed was not recorded, for there were significant rotational and translational resonant body artifacts in this direction.[14]

The frequency response of the entire system in the head-foot axis was flat from 1 to 25 cycles per second, and usable to 40 cycles per second. To obtain this frequency response tight coupling of the body to the bed was necessary. This coupling was accomplished by use of a footboard, and by shoulder, chest, and waist straps.

Standardization of the ballistocardiograph was carried out daily. After the Sanborn Poly-Viso was allowed to warm up for a period of 30 minutes, a 100-pound loading weight was placed upon the bed platform. The bed was suspended, and the bridge balance of the strain-gage amplifier was balanced. A standardization pendulum (fig. 2) was placed at heart level on the 100-pound loaded bed with the ballistic pendulum free to move in the head-foot axis. The total weight of the pendulum and its housing was 4,400 Gm.; the effective weight of the ballistic part of the pendulum, including the arm weight, was 1,568 Gm. With the paper speed of the Sanborn Poly-Viso running at 5 mm. per second, and the strain-gage attenuation switch set at the "× 4" position, the ballistic pendulum was set free from an 11.5-degree angle, which the arm of the pendulum made with a vertical line passing through the central axis. The pendulum delivered approximately 286,000 dynes at each turning point of its swing. The sensitivity of the strain-gage amplifier was adjusted so that the total amplitude between the trough and peak of the tenth recorded swing was 21.5 mm. (fig. 2). The amplitude of the trough-to-peak deflection represented the force delivered by the pendulum at two consecutive turning points in its swing. Thus, a 21.5-mm. deflection was equivalent to about 572,000 dynes when the bed was loaded with 100 pounds. A calibration curve, which revealed the relationship between loading weight and amplitude of the ballistocardiographic deflection, indicated that there was a 35 per cent curvilinear diminution in the over-all acceleration amplitude as the weight on the bed was increased from 140 to 220 pounds. This 35 per cent diminution in amplitude is accurate to within 1.5 per cent of the theoretic calculated value for this 80-pound weight change.

Procedure

The actual recording of a ballistocardiogram on a subject was as follows. After approximately a 2-minute rest period, the subject was placed on the bed platform and coupled to the bed by the footboard and straps. Electrocardiographic leads were attached to the limbs, and an Infraton pulse-wave recorder* was placed over the right carotid artery. The bed was suspended, and the strain-gage attenuation switch set at "× 1." The paper speed was run at 50 mm. per second, and a simultaneous recording of the electrocardiogram (lead II), head-foot ballistocardiogram, and carotid pulse was obtained during a 10-second period with respiration held in the mid phase. The total procedure for each subject lasted less than 5 minutes. A ballistocardiographic recording on a healthy 22-year-old subject is presented in figure 3.

Ballistocardiographic Analysis

The standard nomenclature[9, 18] for labeling the ballistocardiographic deflections was used throughout this paper. A labeled schematic diagram of an acceleratory ballistocardiogram and simultaneous electrocardiogram is shown in figure 4.

Measurements

An arbitrary baseline for each ballistocardiographic complex was assumed to lie along the horizontal line that passes through the top of the H wave. On each ballistocardiogram the fol-

*Made by Medical Electronics Development Company, Great Neck, New York.

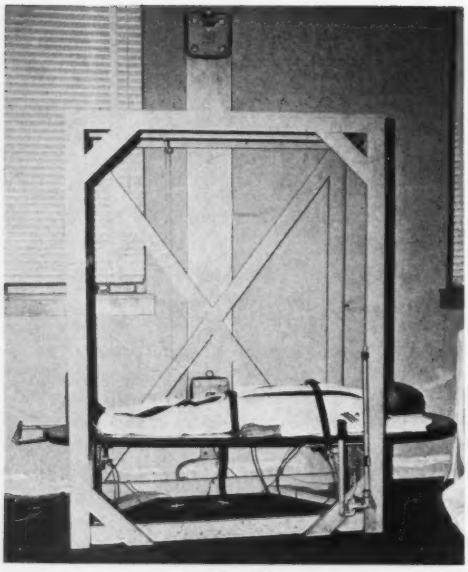


Figure 1

Photograph of the ultra-low frequency acceleration ballistocardiograph. The bed platform is suspended from the wooden frame by three wires. The subject is coupled to the bed by the use of a footboard, and by shoulder, chest, and waist straps.

lowing measurements were made on three consecutive complexes, and the average value was obtained:

1. HI angle—the acute angle that the slope of the ejection deflection (HI wave) made with a true vertical passing through the H point was measured to the nearest 0.5 degree.

2. HI, HJ, HK, amplitudes—the total vertical amplitudes from the H baseline to the I, J, and K points were measured to the nearest millimeter. These amplitudes were converted to absolute units of force in dynes.*

3. HK/HI ratio—the ratio was obtained by dividing the HK amplitude by the HI amplitude.

4. Q-H time—the time duration from the Q wave of the simultaneous electrocardiogram to the H point of the ballistocardiogram was measured to the nearest 0.01 second.

5. H-Jp, H-L times—the time durations from the H point to the peak of the J wave (Jp) and the L point were measured to the nearest 0.01 second.

Descriptions

There were a number of characteristics of the ballistocardiogram that did not lend themselves to precise measurement. When these characteristics were described, however, pertinent aspects of the ballistocardiogram were elucidated. The following groups of arbitrary criteria were set up to describe more completely the ballistocardiographic complex. In almost every case the three consecutive patterns analyzed were nearly identical.

1. Contour of the I-J-K complex—the over-all sharpness of the ballistocardiographic deflections at the I-J-K points was graded according to the following scale:

Contour 1—the three components of a given complex were rounded with no sharp points at the changes in deflection.

Contour 2—two components of a given complex were rounded, and one component had a relatively sharp change in deflection; the over-all pattern was more rounded than sharp.

Contour 3—one component of a given complex was rounded, and two components had relatively sharp changes in deflection; the over-all pattern was more sharp than rounded.

Contour 4—the three components of a complex had sharp changes in deflection, but not markedly so.

Contour 5—all components of a given complex showed very sharp changes in deflection.

2. Ejection pattern—the HI ejection wave was described as being either straight, interrupted, concave, or convex in shape; notation was made when the I wave was flat, or if an I+ wave[9] was present.

3. J wave—the predominant shape of the J wave was described as monophasic, biphasic, triphasic, or serrated; notation was made when a J_d wave[9] was present.

4. Approximate amplitude of the LM, diastolic, and GH waves—the LM and GH amplitudes were obtained by measuring to the nearest millimeter the vertical distance occupied by these waves. The diastolic wave amplitude refers to the maximum vertical deflection in the sinusoidal wave pattern that follows the MN upstroke in each ballistocardiographic complex. The average amplitude of the LM, diastolic, and GH waves, obtained from the measurement of three consecutive patterns, was graded as follows: small—the average amplitude 3 mm. or less; medium—the average amplitude 3+ to 6 mm.; and large—the average amplitude greater than 6 mm.

The total analysis of a ballistocardiogram by this method consisted of seven quantitative measurements and six descriptive terms (fig. 4). The heart rate was calculated from the measured time interval between the first two of the three consecutive complexes analyzed in each tracing. The

*See Appendix I.

analysis of an entire ballistocardiographic tracing required about three to five minutes. From these recorded data the ballistocardiographic pattern can be visualized, and a very accurate reproduction of the original ballistocardiogram can be constructed.

Electrocardiographic Analysis

Standard analysis of the electrocardiograms of the 307 subjects was made with the following measurements noted: P-R interval, QRS duration, frontal plane QRS and T axes, frontal plane QRS-T angle, and amplitude of S in V_2 plus R in V_5. An electrocardiogram was read as abnormal if (1) S-T depression of greater than 1 mm. was present in any lead; (2) generalized low-voltage T waves were present with flat to inverted T waves in leads I, V_5, or V_6; (3) left axis deviation beyond minus 60° was present; (4) a pathologic Q wave in any lead was seen. Thus, an electrocardiogram read as abnormal by these criteria strongly indicated coronary artery disease. In the series of subjects studied, no patterns of bundle-branch block were present.

Results

Change in the Ballistocardiographic Pattern with Age

The mean measurements, ranges, and standard deviations obtained from the analysis of the ballistocardiograms in 307 male subjects are presented by age groups in table 2. As one would expect, the heart rate increased slightly with age; it was 10 beats per minute faster in the oldest as compared with the youngest age group. The mean HI angle remained rather constant and there was no significant change with age. The mean HI and HJ forces (dynes) and the mean HK/HI ratio showed a progressive, almost linear, age-related change. The HI and HJ values decreased with age, whereas the HK/HI ratio increased (fig. 5). Some of the effects of age on the ballistocardiogram are apparent from these graphs.

The mean HK value showed a slight non-progressive increase with age. The mean value for the Q-H time interval remained the same in all four groups, yet the spread of values was slightly greater in the older ages. The mean H-Jp time duration was 0.01 second longer in the oldest group than in the other three age levels. The H-L time interval was 0.02 second shorter in the oldest three age groups than in the youngest. Also, the mean systolic ballistocardiographic contour (1-rounded, 5-sharp) became progressively more rounded with age.

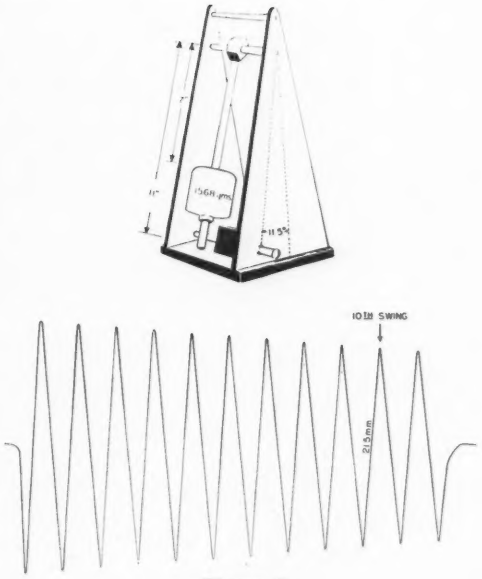


Figure 2

Top. Diagram of the standardization pendulum. The frame and the shaft of the pendulum are made of aluminum. The ballistic portion of the pendulum is a 2½ by 2 inch copper tubing filled with lead. The shaft of the pendulum swings freely about the axis on a ball bearing joint. The pendulum delivers about 286,000 dynes at each turning point in its swing. Bottom. Diagram of the standardization tracing produced by the ballistic pendulum swinging freely in the head-foot axis on the ballistocardiographic bed. The vertical distance between the trough and peak of the tenth recorded swing measures 21.5 mm.

In table 3 is presented the frequency of the various ballistocardiographic deflections. An interruption in the ejection deflection (HI wave) was observed in one third of the individuals in the 18 to 24 age group, and it was a considerably more frequent occurrence in this group than in any of the other age levels. In almost all cases the interruption in the HI wave occurred 0.03 second or less after the H point, and the interrupted HI wave usually was associated with a relatively wide HI angle (greater than 12 degrees). An interrup-

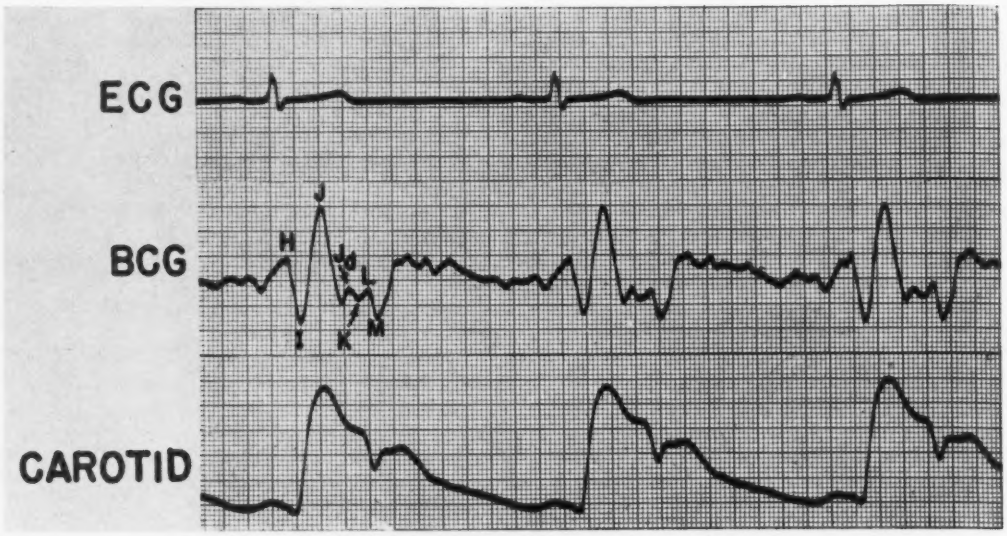


Figure 3

Simultaneously recorded electrocardiogram, ballistocardiogram, and carotid pulse taken on a 22-year-old man. The paper speed is 50 mm. per second and the heavy time lines are at 0.10 second intervals. The first pattern is labeled, and the J_d wave is clearly evident on this tracing.

tion 0.04 second or greater after H rarely appeared. Concave and convex HI waves occurred infrequently in all age groups. An I+ deflection as well as a flat I wave were seen most frequently in the older ages. There were three individuals in the 18 to 24 age group whose records showed an I+ wave. In each case the I+ deflection was 0.03 second after H and the HI angle was relatively acute, being less than 7.2 degrees. In the oldest age group there were four individuals with an I+ wave. In these individuals the I+ wave was 0.04 to 0.06 second after H and this late I+ deflection was associated with a wide HI angle of 12.0 degrees or greater.

The J wave was observed to be completely monophasic in the youngest age group, and it became somewhat polyphasic with age. The J_d wave was a very discrete entity in about two fifths of the cases in the 18 to 24 age group, and always occurred later than 0.22 second after H. When the J_d wave was present in the oldest age group, however, it measured 0.16 to 0.18 second after H and appeared as a change in deflection on the descending limb of the JK wave. When a late discrete J_d wave was present, the J wave itself showed the same slope on the ascending and descending limbs. However, when the J_d wave was not discernible, the J contour was skewed on its descending limb as if another wave (J_d) had been incorporated under it.

Table 3 also reveals that the LM wave was frequently smaller in the oldest age group than in the youngest. However, the presystolic GH wave showed precisely the opposite change with age. The diastolic wave size was generally small, and the frequency of its occurrence did not change with age.

From the composite measurements and descriptions presented in tables 2 and 3, a ballistocardiogram typical of each age group was drawn (fig. 6). The subtle change in the ballistocardiographic pattern with age can best be appreciated by closely examining the progressive alteration in the various deflections and waves in these redrawn complexes. It should be emphasized that these patterns were drawn from the mean values obtained at each age level. The difference in the mean weight

Table 2

Ballistocardiographic Measurements

	Age groups			
	18-24 Mean ± S.D. Range	25-34 Mean ± S.D. Range	35-44 Mean ± S.D. Range	45-54 Mean ± S.D. Range
Heart rate	59 ± 10.7 40-86	65 ± 10.8 47-103	66 ± 11.3 50-110	69 ± 11.9 42-97
HI angle (degrees)	12.5 ± 4.6 5.7-23.8	10.9 ± 3.0 4.7-17.0	11.7 ± 5.0 5.0-35.6	12.5 ± 4.4 4.7-24.7
HI force ($x10^3$ dynes)	135.3 ± 32.7 68.3-267.4	134.6 ± 32.2 74.2-214.2	130.7 ± 35.7 66.9-227.9	116.1 ± 34.5 47.9-198.4
HJ force ($x10^3$ dynes)	95.6 ± 27.1 51.6-211.3	89.5 ± 32.2 29.7-135.8	66.4 ± 29.3 3.0-139.1	55.4 ± 33.7 0.0-137.1
HK force ($x10^3$ dynes)	84.3 ± 25.3 19.4-151.6	95.3 ± 31.0 22.6-144.3	103.1 ± 34.4 45.8-229.1	103.8 ± 36.4 50.4-212.0
HK/HI ratio	0.62 ± 0.13 0.41-1.00	0.72 ± 0.22 0.27-1.39	0.82 ± 0.25 0.44-1.99	0.93 ± 0.30 0.54-1.83
Q-H time (sec.)	0.09 ± 0.01 0.05-0.12	0.09 ± 0.01 0.05-0.12	0.09 ± 0.02 0.05-0.12	0.09 ± 0.02 0.05-0.13
H-Jp time (sec.)	0.14 ± 0.01 0.12-0.18	0.14 ± 0.01 0.11-0.17	0.14 ± 0.02 0.09-0.20	0.15 ± 0.02 0.12-0.20
H-L time (sec.)	0.34 ± 0.02 0.28-0.38	0.32 ± 0.02 0.28-0.36	0.32 ± 0.03 0.22-0.39	0.32 ± 0.03 0.24-0.37
Contour	3.7 ± 0.52 2-5	3.4 ± 0.75 2-4	3.2 ± 0.76 2-5	3.0 ± 0.71 2-4

for the four age groups was less than 9 pounds. Thus, the weight discrepancy between age groups is not a factor causing the ballistocardiographic change with age in these redrawn complexes.

Criteria for Ballistocardiographic Abnormality

The mean values, standard deviations, and frequency occurrence of the various ballistocardiographic deflections at four age levels have been presented in the previous section. Many of the ballistocardiographic deflections changed progressively with age (figs. 5 and 6; tables 2 and 3). Since rheumatic heart disease and hypertension were absent in the population under study, then it is highly probable that the changing ballistocardiographic pattern reflected functional cardiovascular aging.

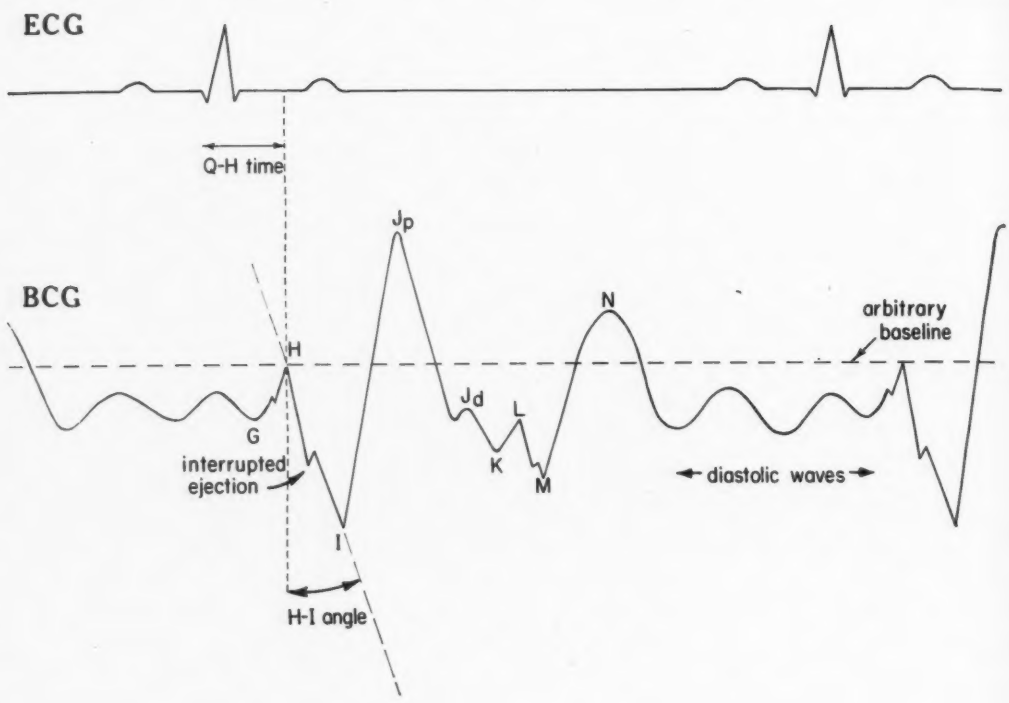
The criteria for ballistocardiographic abnormality were derived from the three ballistocardiographic measurements (HI, HJ, HK/HI) which progressively changed with age. A ballistocardiographic measurement (HI, HJ, or HK/HI) was defined as abnormal if it was two standard deviations or greater from the mean value at age 26, in the direction of the measurement change with age (fig. 7, table 4). An abnormal ballistocardiogram was one containing one or more of the abnormal measurements that indicated advanced or accelerated cardiovascular aging.

There are three possible gradations of ballistocardiographic abnormality depending upon the number of "abnormal" measurements in a given tracing. The degree of ballistocardiographic abnormality was classified arbitrarily as grade I, II, or III. A grade-I abnormality had only one abnormal measurement present in the ballistocardiogram; grades II and III had combinations of two or three abnormal measurements, respectively. When two or more abnormal measurements occurred together in the same tracing, it seemed reasonable to conclude that a more severe degree of accelerated cardiovascular aging existed.

By means of these criteria of abnormality, ballistocardiographic patterns were drawn to represent the kinds of abnormality that could theoretically be obtained (fig. 8).

The Abnormal Ballistocardiogram

There were 61 persons in this overtly



BCG ANALYSIS

HI = 12 mm	HI angle = 10.0°	Contour — 4
HJ = 10 mm	Q-H = 0.09 sec.	Ejection — interrupted J wave — monophasic
HK = 6 mm	H-Jp = 0.14 sec.	LM wave — medium Diastolic wave — small
HK/HI = 0.50	H-L = 0.32 sec.	GH wave — medium

Figure 4

Skematic labeled diagram of the simultaneously recorded electrocardiogram and ballistocardiogram. A method of analyzing the ballistocardiogram is presented in the lower portion of the figure.

healthy population with abnormal ballistocardiograms according to our criteria. The percentage of all individuals exhibiting one, two, and three abnormal ballistocardiographic measurements at the various age levels is presented in table 5.

The percentage of individuals with a grade-I abnormality increased progressively with age. The more severe ballistocardiographic abnormalities (grades II and III) began to develop in the fifth decade and gave the oldest age group a relative predominance of abnormal patterns. These results suggested a ballistocardiographic conversion with age from grade I to grade II, and from grade II to grade III.

In the 49 grade I cases (table 5) there were 25 HJ, 21 HK/HI, and 3 HI abnormalities.

In the 11 grade-II cases, the combined HJ-HK/HI abnormality predominated. The frequent occurrence (14.6 per cent) of more than one ballistocardiographic abnormality in the 45 to 54 age group suggested a common factor etiologically responsible for the combination of abnormalities.

Figure 9 is a smoothly drawn graph plotted from the data presented in table 5. A grade-I ballistocardiographic abnormality was evident in 16 per cent of the population by age 35. A grade-II abnormality was present in about 16.5 per cent of the individuals by age 50. At age 50, about 40 per cent of the population had no evidence of ballistocardiographic abnormality.

On the assumption that an abnormal ballistocardiogram deteriorates from grade I, through grade II, to grade III, then from the graphs in figure 9 the attack rate for a grade-I abnormality and the conversion rate from grade I to grade II can be calculated* (fig. 10). There appears to be a rather constant attack rate before age 40 and a sharp increase thereafter. The rate of conversion to a grade-II abnormality showed a very significant rise in the fifth decade. One cannot say from this graph whether the individuals who converted to grade II in the fifth decade were the ones in whom a grade-I abnormality developed during the early portion of the 20 to 39 age period. That is, there may be a 15- to 20-year lag between the development of a grade-I abnormality and the conversion to grade II, but this is not the only possibility.

The electrocardiograms of all (fig. 10) 307 subjects were analyzed, and the mean values for the various measurements and the frequency occurrence of an abnormal electrocardiogram are presented in table 6. An abnormal electrocardiogram indicative of coronary artery disease was obtained from five individuals (9.3 per cent) in the 35 to 44 age group, and from 8 individuals (19.5 per cent) in the 45 to 54 group. In table 7 are presented the ballistocardiographic analyses of the 13 subjects with abnormal electrocardiograms. Ten of them (77 per cent) had one or more ballistocardiographic measurements that met the criteria of abnormality. Thus, a high correlation existed between an abnormal ballistocardiogram and electrocardiographic evidence of coronary artery disease in this group of individuals.

Table 3

Per Cent Distribution of Various Types of Ballistocardiographic Deflections

	Age groups			
	18-24	25-34	35-44	45-54
Ejection HI wave:				
Straight	63.0	78.7	76.6	75.5
Interrupted	33.3	19.5	21.0	22.0
Concave	0.0	0.0	0.8	0.0
Convex	3.7	1.8	1.6	2.5
I wave:				
I+	3.7	0.0	10.9	14.6
I flat	1.2	5.4	0.0	12.2
J wave:				
Monophasic	100.0	100.0	86.0	78.1
Biphasic	0.0	0.0	12.4	19.5
Triphasic	0.0	0.0	0.8	0.0
Serrated	0.0	0.0	0.8	2.4
Jd	38.3	10.7	12.4	7.3
LM wave:				
Small	18.6	35.7	40.3	41.5
Medium	40.7	41.1	42.6	46.3
Large	40.7	23.2	17.1	12.3
Diastolic wave:				
Small	61.7	64.3	58.1	60.2
Medium	35.8	35.7	34.9	34.9
Large	2.5	0.0	7.0	4.9
GH waves:				
Small	25.9	19.6	10.1	7.3
Medium	54.3	58.9	57.4	53.7
Large	19.8	21.5	32.5	39.0

Discussion

The cardiovascular aging process has been evaluated ballistocardiographically in 307 men. The percentage of individuals with the initial appearance of accelerated cardiovascular aging increased progressively with age. Also, a more severe degree of aging appeared significantly for the first time in the fifth decade. The frequency-age distribution of the grades of ballistocardiographic abnormality seen in the present study were remarkably similar to the incidence-severity distribution of coronary artery disease reported in a number of necropsy studies in the literature. Enos et al.[7] in their study of the incidence of coronary disease in U. S. soldiers killed in action in Korea showed that in the 20 to 30 age

*See Appendix II.

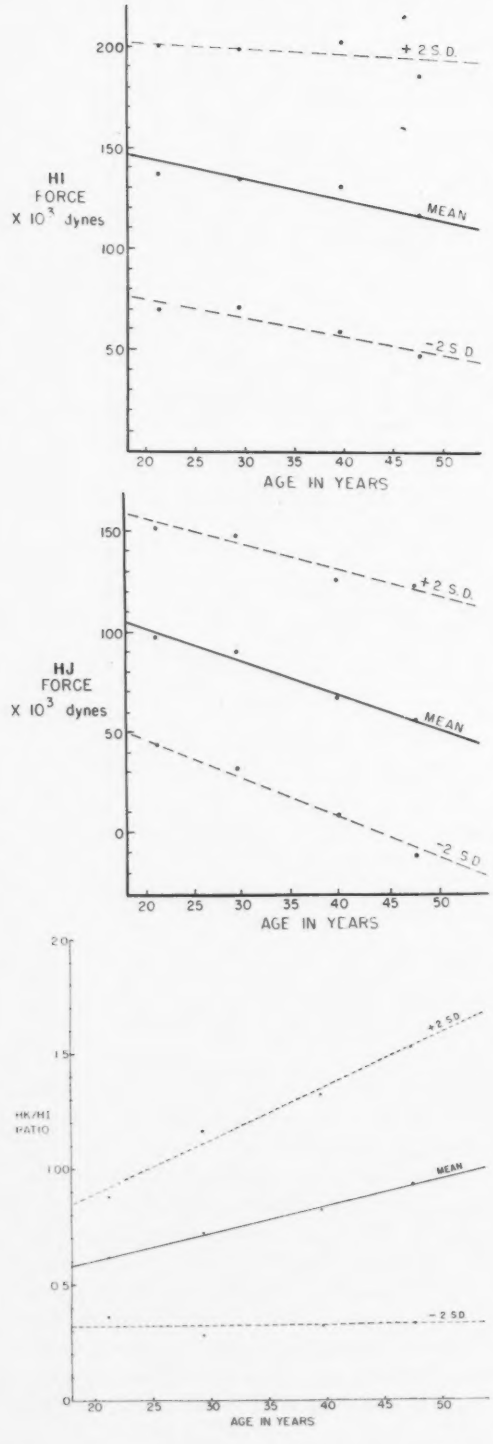


Table 4

Criteria for Ballistocardiographic Abnormality

HI (dynes × 10^3)	HJ (dynes × 10^3)	HK/HI (ratio)
<69.1	<35.1	>1.02

group range about 77 per cent of the hearts showed some gross evidence of significant coronary atherosclerosis, with 10 per cent showing advanced coronary artery disease. Spain et al.[6] in their consecutive autopsy series on 73 white men killed suddenly by trauma showed that severe coronary artery disease (grades 3 and 4 on a scale of 4) began to increase between ages 36 and 40, and then rose rapidly to involve 28 per cent of the population in the 41 to 55 age range. A graph relating the frequency of severe coronary atherosclerosis to age can be drawn from Spain's[6] data, and this curve is similar in shape to the incidence graph of the grade-II ballistocardiographic abnormality presented in figure 9 of the present study. White et al.[19] as well as Saphir et al.[20] showed that the most striking increase in the incidence of severe coronary atherosclerosis occurred in the fifth decade, a finding similar to the frequency of a grade-II ballistocardiographic abnormality seen in the present study.

There have been a large number of ballistocardiographic studies that demonstrated a relationship between a qualitatively abnormal tracing and overt symptomatology of coronary artery disease.[21–33] Unfortunately, the majority of these studies have been done with a ballistocardiographic instrument that did not meet basic theoretical considerations of design.[10–14] Thus, the results of those studies are not strictly comparable with the data presented in this paper. Suffice it to say, there is

Figure 5

Progressive change in the HI, HJ, HK/HI values with age. The solid lines are the regressions for the mean. The dotted lines are the lines of best fit through the values two standard deviations from the mean. Top. Progressive diminution in the HI force. Middle. Progressive diminution in the HJ force. Bottom. Progressive increase in the HK/HI ratio.

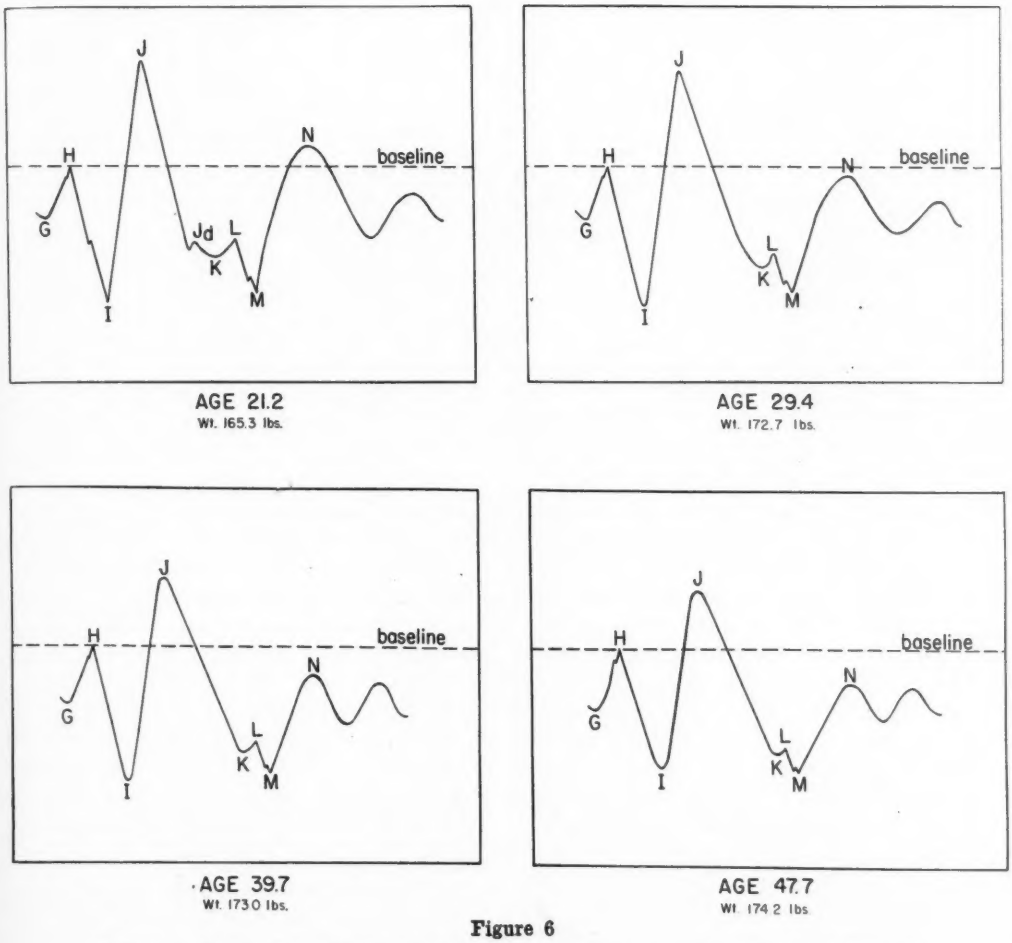


Figure 6

Ballistocardiographic patterns constructed from the mean measurements at four age levels. Notice the progressive diminution in the HJ amplitude and the increase in the HK/HI ratio. Also, the over-all contour of the complexes becomes more rounded with age.

general agreement that regardless of the ballistocardiographic technic used, gross alterations in pattern are present with increasing frequency beginning at age 50; also, an abnormal tracing before age 50 seems to have prognostic significance. More recently, Smith et al.,[34] using a ballistocardiographic instrument similar to the one described in this study, demonstrated a flat, low-amplitude J wave on the acceleratory tracing of a 45-year-old pilot in whom a myocardial infarction developed 2 years later. The ballistocardiogram on this patient was presented in a photograph and, with the assumption that the individual was of normal weight, it corresponds to at least a grade-I abnormality by the present criteria.

There are many factors associated with advancing chronologic age that must be considered in evaluating the cause for the ballistocardiographic change with age. The possible alteration in the ballistocardiogram with varying heart rates is one of the considerations, since there was slight acceleration in

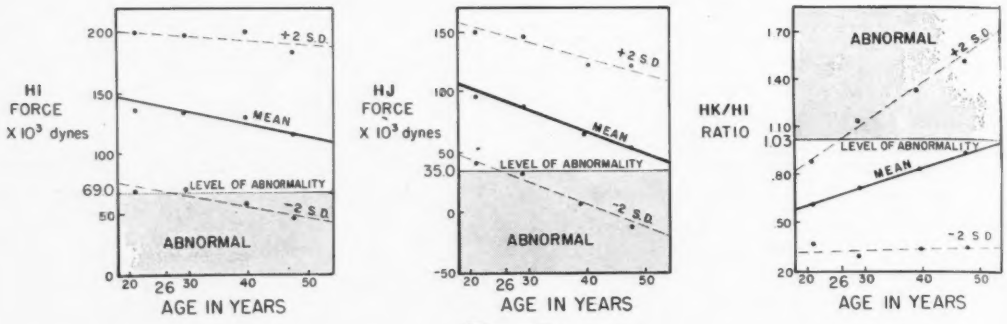


Figure 7

The arbitrary levels of abnormality for the HI, HJ, HK/HI measurements. In each case the level of abnormality was set at two standard deviations from the mean at age 26, in the direction of the change with age.

the heart rate with advancing years. Frederick and Eddleman[35] pointed out that the delivery of the stroke volume and its interaction with the functional state of the vascular tree determined the form of the ballistocardiographic complex. Normal variation in the heart rate due to the interplay of autonomic influences on the sinoatrial node would not be expected to alter significantly the pattern of cardiac contraction or the peripheral vascular resistance. Extremes in heart rate, however, probably would be associated with a change in the basic ballistocardiographic pattern due to an underlying alteration in the circulatory hemodynamics. Since the total average increase in heart rate between the youngest and oldest age groups in this study was only 10 beats per minute, it is unlikely that this minor acceleration in heart rate played any role in the ballistocardiographic change with age.

The alteration in the ballistocardiographic pattern with changes in body weight is pertinent. The amplitude of the ballistocardiographic deflection is inversely proportional to the total bed mass. Thus, as the weight on the ballistocardiographic bed was increased from 140 to 220 pounds, there was a 36 per cent diminution in over-all amplitude of the recorded pattern. This weight-amplitude relationship was taken into consideration and each acceleration amplitude was converted into absolute units of force in dynes.

It is conceivable that the effect of the aging process on the turgor or resiliency of the supporting structures of the body played a role in altering the ballistocardiographic complex in the older age groups. Starr,[36-38] in his necropsy perfusion experiments, produced a wide range of ballistocardiographic patterns in the same individual simply by altering the stroke force, the volume of ejected blood, and the rate of application of the delivered force. Frederick and Eddleman[35] believed that the forces operating strictly within the cardiovascular system were the major determinants of the ballistocardiographic pattern. The vibromechanical properties of the body were studied by Tannenbaum et al.,[13] who demonstrated that the inherent frequency of the body mass was not correlated significantly with age or anthrometric measurements. There was a high correlation, however, between natural body damping and age, and this factor may be one of the extracardiac phenomena chronologically related to the changing ballistocardiographic pattern.

A consideration of major importance is the changing direction of the cardiac force vector with age. A number of investigators[39-41] have shown that the ballistic systolic forces are directed longitudinally in young persons and have a more lateral representation in the older age groups. In the present study only longitudinal (head-foot) forces were recorded. All ballistocardiograms at the present time have

Table 5

Per Cent Distribution of Individuals with Three Grades of Ballistocardiographic Abnormality

BCG abnormality	Age groups 18-24 (21.2)	25-34 (29.4)	35-44 (39.7)	45-54 (47.7)
Grade I	1.2	8.9	22.5	34.1
Grade II	0.0	1.8	3.9	12.2
Grade III	0.0	0.0	0.0	2.4
Total (I + II + III)	1.2	10.7	26.4	48.7

Table 6

Electrocardiographic Findings: Mean Measurements and the Percentage of Individuals with Abnormal Tracings

	Age groups 18-24	25-34	35-44	45-54
PR interval (sec.)	0.16	0.16	0.16	0.16
QRS duration (sec.)	0.08	0.08	0.08	0.08
QRS axis (degrees)	66.2	58.4	42.6	41.0
T axis (degrees)	48.7	41.5	38.5	37.7
QRS-T angle (degrees)	26.1	24.9	22.3	22.3
$Sv_2 + Rv_5$ (mm.)	29.1	23.6	22.1	19.9
Abnormal ECG* (per cent)	0.0	0.0	3.9	19.5

*Criteria of abnormality defined in section on methods.

resonant body artifacts in the lateral recording of motion,[14] and thus the conclusions drawn from the lateral ballistocardiogram must be interpreted cautiously. Scarborough et al.,[39] working with the high-frequency Starr bed, showed that the IJ vector force changed from a head-foot to a lateral direction with increasing age. March[41] demonstrated similar results with Dock direct-body electromagnetic pickup. Honig and Tenney,[42] using an aperiodic ballistocardiogram with properties similar to the Reeves instrument, reiterated the changing position of the frontal plane vector from longitudinal to lateral orientation with age. The etiology of this directional change in the systolic ballistic forces with age has not been explained. It is unlikely that it represents a simple anatomic shift in the position of the heart.[40] More likely, it probably represents a circulatory aging process in terms of altered cardiac contractility and vessel distensibility.

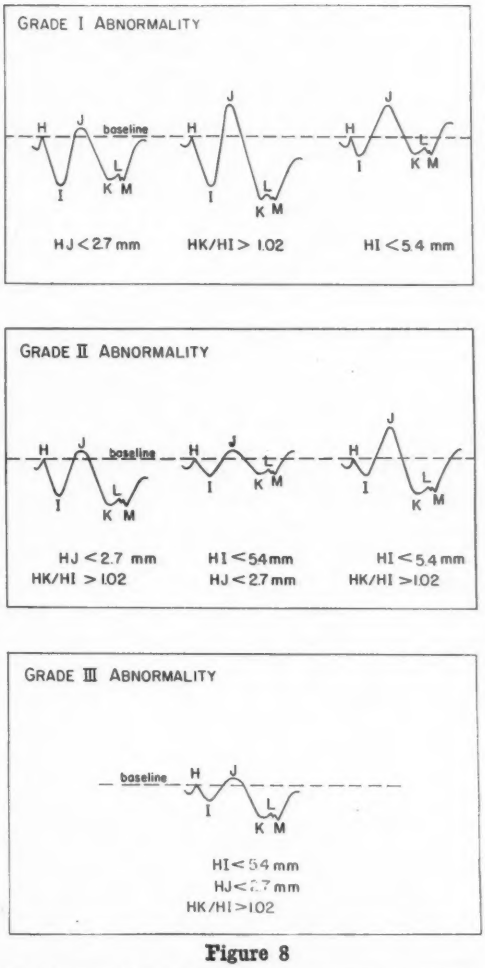


Figure 8

Ballistocardiographic patterns showing the three grades of abnormality. The tracings were constructed with one, two, and three measurements meeting the criteria of abnormality for a subject weighing 220 pounds or less.

Starr[43] introduced the concept of "presbycardia" to explain the changing ballistocardiographic pattern with age in the so-called normal person. He thought that the heart muscle became less powerful, i.e., the work output per unit of time diminished, in the older years. The etiology of this diminished power may be due to the effects of subclinical coronary artery disease, as coronary atherosclerosis is a progressive process in the age

Table 7

Ballistocardiographic Patterns on 13 Subjects with Electrocardiographic Evidence of Coronary Artery Disease

Subject	Age (yrs.)	Ht. (inches)	Wt. (lb.)	Heart Rate	HI Angle (degrees)	Force ($\times 10^3$ dynes) HI	HJ	HK	HK/HI	Time (sec.) Q-H	H-Jp	H-L	Polyphasic J wave	Contour (scale 1-5)	Grade BCG Abn.	ECG
H. H. R.	36	68	152	58	7.5	120.1	78.6	75.0	0.62	0.10	0.13	0.34	—	3	0	Generalized low voltage T waves with flat T in I; ½ mm ST segment depression in II, aV_F, and III after exercise.
H. R. B.	37	68	186	110	14.0	87.0	62.0	112.1	1.28*	0.09	0.14	0.23	—	3	I	Generalized low voltage T waves with flat T in V_{5-6}.
J. B. D.	38	67	153	57	11.8	90.8	24.5*	79.0	0.87	0.11	0.12	0.31	—	4	I	Generalized low voltage T waves with flat T in V_{5-6}.
H. E. J.	41	70	175	63	11.8	182.1	120.3	85.4	0.46	0.06	0.15	0.34	—	3	0	Generalized low voltage T waves with flat T in I, V_{5-6}; negative exercise tests.
T. G. L.	41	68	177	86	11.3	90.4	69.6	114.3	1.26*	0.10	0.17	0.27	—	2	I	Generalized low voltage T waves with inverted T in V_{5-6}; positive exercise tests.
Q. R. N.	45	69	133	66	24.7	48.0*	101.6	50.4	1.05*	0.07	0.16	0.35	+	3	II	1 mm ST segment depression on the resting tracing in aVF, III, V_6.
G. H.	45	70	180	71	7.3	84.4	42.2	123.5	1.46*	0.11	0.14	0.32	—	2	I	Q in II, aVF, and III; generalized low voltage T waves.
J. W. F.	47	70	211	64	16.8	131.0	40.4	138.3	1.06*	0.09	0.17	0.35	—	3	I	Generalized low voltage T waves with flat T in I, V_6.
J. F. B.	48	68	199	97	20.5	147.1	57.9	212.0	1.44*	0.09	0.17	0.27	—	4	I	Generalized low voltage T waves with flat T in V_{5-6}; 1 mm ST segment depression in II on the resting tracing.
I. M. P.	48	68	162	79	16.8	64.1*	38.3	64.1	1.00	0.10	0.13	0.24	—	3	I	1-1½ mm ST segment depression on the resting tracing in II, aVF, and III.
E. J. L.	49	67	178	75	13.2	111.8	38.6	107.5	0.96	0.07	0.17	0.33	+	2	0	Generalized low voltage T waves with flat T in I.
B. W.W.	50	71	200	94	12.0	154.8	15.1*	201.4	1.30*	0.10	0.13	0.24	—	3	II	Generalized low voltage T waves with flat T in I, V_{5-6}.
V. N. P.	52	67	165	70	35.6	48.7*	48.8	90.6	1.86*	0.09	0.14	0.27	—	3	II	Low flat T wave in V_6; loss of R wave with QS complex in V_{1-2}.

*Indicates that the values met the criteria of abnormality.

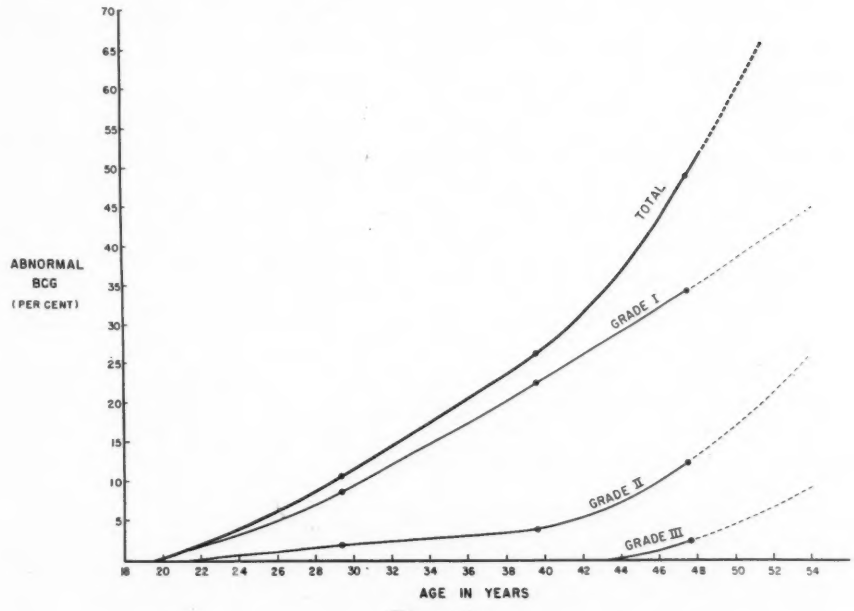


Figure 9

The frequency occurrence by age of the three grades of ballistocardiographic abnormality. The points on this graph were obtained from the data presented in table 5. The dotted lines represent extension of the curves beyond the last recorded data point at age 47.7.

group studied. It seems reasonable that the pattern of myocardial contractility would be altered either from relative coronary insufficiency or from secondary myocardial fibrosis. Thus, the ballistocardiographic change with age demonstrated in this overtly healthy population may represent the effects of diminished cardiac power from progressive coronary atherosclerosis. If this is the case, then an abnormal ballistocardiogram may be a sensitive indicator of early, subclinical coronary artery disease.

There were 13 individuals in the population with electrocardiographic evidence of coronary artery disease. Ten of them had an abnormal ballistocardiogram, and this association lends further support to the possible relationship between an abnormal ballistocardiogram and coronary artery disease. Three in this group of 13 had ballistocardiograms that were entirely normal in all respects. It is possible that the ballistocardiogram in these three subjects failed to reveal accelerated cardiovascular aging coincident with coronary artery disease. An equally good possibility is that coronary artery disease was not present even though the electrocardiogram was "abnormal." Although these three persons had generalized low-voltage T waves in their resting electrocardiograms, their records showed a normal QRS axis, a narrow QRS-T angle, and no S-T abnormality. One of the three subjects (H.E.J.) had negative exercise tests, which included a double Master's step test, and 3- and 5-minute Harvard step tests.[44] Another (H.H.R.) had a borderline response to a 3-minute Harvard exercise test with an 0.5 mm. S-T depression in leads II, aV_F, and III 3 minutes after the completion of the exercise. It is entirely possible that all three subjects with normal ballistocardiograms did not have coronary artery disease, and the generalized low-voltage T waves in their resting electrocardiograms had another etiology. Only long-term follow-up of these persons will solve the question.

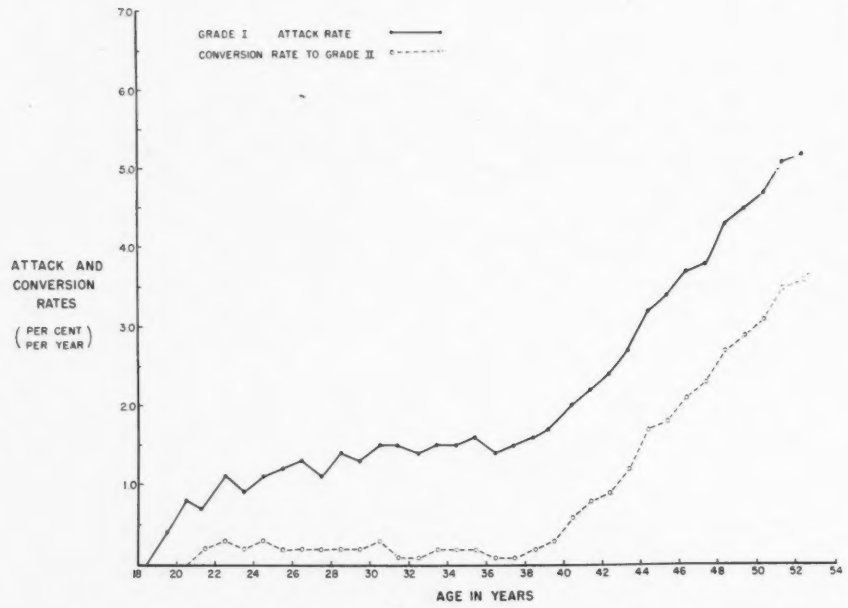


Figure 10

Attack rate for grade I and conversion rate to grade-II ballistocardiographic abnormality. A grade-I abnormality shows a rather constant attack rate in the 20 to 39 age period, and an accelerated attack rate after age 40. The rate of conversion to a grade-II abnormality increases significantly in the fifth decade.

If a relationship between an abnormal ballistocardiogram and coronary artery disease exists, then the ballistocardiogram may be useful as a predictor of underlying ischemic heart disease. Recently, a 37-year-old pilot was seen for cardiac evaluation, and 3 weeks after the examination he died of an acute myocardial infarction. The following is a case report of this person with pertinent clinical, ballistocardiographic, and necropsy findings.

R. W. B. (no. 3648, U.S.N.S.A.M.) was a 37-year-old male aviator seen on June 30, 1959, for cardiac evaluation. There were no recent symptoms. However, 11 months previously he had experienced a very transient episode of hemianesthesia and partial aphasia for which no explanation could be found. Electroencephalogram and carotid angiogram were normal, as were all other clinical studies at that time.

Physical examination was entirely normal except for slightly increased arterial light reflex in the ocular fundi. The carotid pulses were full and equal bilaterally. Cardiac examination was normal, with a blood pressure of 144/88 mm. Hg in the supine position. Neurologic examination revealed no abnormality. The patient's weight was 168 pounds, height 71.5 inches.

Laboratory data revealed a normal resting and exercise electrocardiogram (3-minute Harvard step test, one step every 3 seconds). Cardiac x-rays and fluoroscopy were normal. Blood lipid studies revealed a fasting serum cholesterol of 229 mg. per cent, and an atherogenic index of 74. Ballistocardiogram (fig. 11) showed a grade-II abnormality with significantly divergent HI and HK/HI values ($HI=64.2\times10^3$dynes; $HK/HI=1.54$).

Since the ballistocardiogram was the only abnormality detected, the patient was returned to full-duty status. Three weeks later the patient died suddenly of an acute myocardial infarction. Autopsy findings* revealed extensive coronary atherosclerosis involving both the right and left coronary arteries. About 2 cm. below the ostium of the left coronary there was an acute occlusion of the vessel, probably secondary to hemorrhage below an arteriosclerotic plaque. Myocardial infarction of about 24 hours was present. The in-

*The autopsy was performed by the Pathology Department, Gunter Air Force Hospital, Montgomery, Alabama.

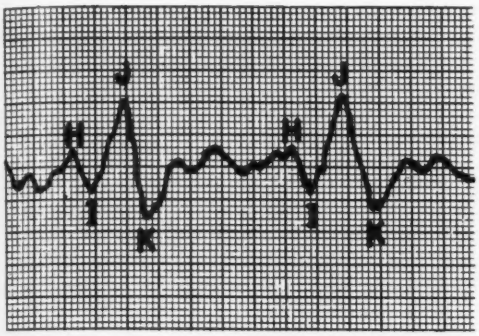


Figure 11

Ballistocardiographic pattern (grade-II abnormality) obtained on an asymptomatic 37-year-old man 3 weeks before a fatal myocardial infarction. Necropsy revealed extensive coronary artery disease.

farction involved principally the posterior area of the ventricular septum. There was no significant atherosclerosis in the remainder of the vascular tree, and the cerebral vessels and both carotid arteries were intact.

This individual had extensive coronary disease that existed long before his acute, fatal myocardial infarction. It is striking that resting and exercise electrocardiograms were entirely normal 3 weeks before his demise. The ballistocardiographic abnormality was the only objective evidence that suggested the presence of accelerated cardiovascular aging.

It should be emphasized that the level of ballistocardiographic abnormality has been arbitrarily set up, and thus it can be altered in the future on the basis of follow-up data. Also, the standards of normality and abnormality were derived from men, and they are not applicable to women, since the ballistocardiogram in women generally shows lower over-all amplitude.[39] The criteria of abnormality in women could be set up, however, in the same manner as was done in this study.

In conclusion, it should be pointed out that the Reeves ultra-low frequency ballistocardiograph is easily constructed, relatively inexpensive, simple to operate, and can be reliably standardized. This system has very accurate test-retest reliability, and essentially the same ballistocardiographic pattern can be obtained on any given individual when repeat tracings are taken. The empiric observations of the ballistocardiographic change with age have been presented. The validity of the relationship between an abnormal ballistocardiogram, accelerated cardiovascular aging, and coronary artery disease requires further substantiation from follow-up studies. If the results presented in this paper stand the test of time, then the possible diagnosis of early subclinical coronary artery disease from an abnormal ballistocardiogram appears promising.

Summary

A clinically adaptable, ultra-low frequency acceleration ballistocardiograph that met all theoretic considerations of biophysical design was used to evaluate the cardiovascular aging process in 307 overtly healthy men aged 18 to 54.

A new practical method for quantitative ballistocardiographic analysis is described, and the changing ballistocardiographic pattern with advancing age is elucidated.

Criteria for ballistocardiographic abnormality are established in terms of accelerated cardiovascular aging, and the degree of abnormality is graded (I-III).

The initial appearance of accelerated cardiovascular aging (grade-I abnormality) was present on the ballistocardiogram in 16 per cent of the population by age 35. A more severe degree of aging (grade II) was evident in 16.5 per cent of the individuals by age 50. There was a rather constant attack rate for the initial development of an abnormal ballistocardiogram (grade I) during the 20 to 39 age period, and an accelerated attack rate after age 40. The rate of conversion to a more severe grade of ballistocardiographic abnormality increased significantly in the fifth decade.

The relationship between an abnormal ballistocardiogram, accelerated cardiovascular aging and coronary artery disease is discussed.

Appendix

I. Conversion of acceleration amplitude measurements to absolute units of force in dynes

It is known that:

$$F = m \times a. \qquad (1)$$

F is force in dynes, m is mass in grams, and a is acceleration in cm./sec.^{2}.

Let M be the mass of the subject in pounds. The total weight of the ballistocardiographic bed with electrocardiographic electrodes is 14 pounds. Then:

$$m = (M + 14) \text{ lbs.} \times \frac{1 \text{ kilo}}{2.2 \text{ lb.}} \times \frac{1000 \text{ Gm.}}{1 \text{ kilo}} \quad (2)$$

$$m = 453.6\ (M + 14). \quad (3)$$

It was found by calibration that 1 mm. of ballistocardiographic amplitude is equal to 0.12 cm./sec.^{2}. Thus,

$$a = 0.12\ A, \quad (4)$$

where A is the ballistocardiographic acceleration amplitude in millimeters.

Combining equations (3) and (4) into the original equation (1), we have:

$$F = 453.6\ (M + 14) \times 0.12\ A \quad (5)$$

$$F = 54.4 \times (M + 14) \times A. \quad (6)$$

II. Derivation of the formulae for calculating attack and conversion rates for ballistocardiographic abnormality.

Let P (i) [Q (j)] be the proportion of persons in the total population who show a grade i [grade j] ballistocardiographic abnormality in the n th [(n+1) th] year, and R (i, j) the proportion of the total population who had a grade i abnormality in the n th year and a grade j abnormality in the (n+1) th year.

In drawing figure 10, it was assumed that:

$$P\ (III) = R(III, III) \quad (1)$$

$$Q\ (III) = R(III, III) + R(II, III) \quad (2)$$

$$P\ (II) = R(II, II) + R(II, III) \quad (3)$$

$$Q\ (II) = R(II, II) + R(I, II) \quad (4)$$

$$P\ (I) = R(I, I) + R(I, II) \quad (5)$$

$$Q\ (I) = R(I, I) + R(O, I) \quad (6)$$

The attack rate, R(O, I), and the conversion rate, R(I, II) were obtained by solving the above six equations with data derived from the graph in figure 9 of the text at yearly intervals between ages 18 and 51.

It was assumed that no one "jumped" a ballistocardiographic grade of abnormality in a year's time. Also, it was assumed that no deaths occurred. Even if the death rate were known and taken into consideration, however, the relative position of these curves (fig. 10) would not be effected.

Acknowledgment

I am deeply grateful to Dr. Ashton Graybiel for his encouragement, enthusiasm, and suggestions, which led to this ballistocardiographic study. I wish to thank Dr. Ronald Malt, who constructed the acceleration ballistocardiograph used in this paper. Also, I am indebted to Dr. Marshall Jones for his assistance in the derivation of the formulae for the calculation of attack and conversion rates.

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SPECIAL ARTICLE

Some Physiopathologic Regularities in the Process of Dying and Resuscitation

By V. A. NEGOVSKY, M.D.

COMPLETE STUDY of the mechanisms of death and resuscitation represents one of the typical trends in the development of modern biology. Investigators were faced with a new class of biological phenomena when the accepted laws and regularities often contradicted the usual concepts of the functions of the living body. A new branch of medical science has come into being, devoted to the physiopathology and treatment of the terminal stages of life.

Investigations pursued at the Laboratory of Resuscitation of the Academy of Medical Sciences of the U.S.S.R. allow certain conclusions to be made on the dynamics of the vital functions during the terminal period and permit recommendation of a definite complex method for the resuscitation of the dying organism. This combination of therapeutic measures consists of transfusion of blood into arteries under pressure in the direction of the heart, artificial respiration, defibrillation with a single condenser discharge and of direct, transthoracic massage of the heart. The choice of the therapeutic method depends on the stage of the terminal period.

Arterial transfusion is one of the leading components of the combined therapy of extreme stages of shock and decompensated blood loss.[1]

Stimulation of nerve endings, chemoreceptors and baroreceptors, found in the vascular walls and in the myocardium, with rhythmical arterial blood transfusion represents an essential factor for restoring the activity of the cardiovascular system in cases of severe shock, agony, and clinical death. Arterial blood transfusion also helps to restore the coronary circulation. The blood, to which glucose, epinephrine, and hydrogen peroxide are added, is injected under pressure in the direction of the heart through one of the peripheral arteries; it reaches the aortic bulb and enters the coronary arteries, thus creating a blood flow in the system of the coronary vessels. The myocardium, suffering from extreme hypoxia, receives the lacking nutrition from the blood, oxygen, and glucose, while the epinephrine stimulates cardiac contractions.

Intravenous injection of blood is far from always being effective during the terminal period, and in a number of cases it aggravates the condition partly through marked dilatation of the heart and the possible development of myocardial atony. If intravenous transfusion is administered before agony sets in, and on condition that the arterial blood pressure remains at a level below 60 mm. Hg but for a short time only, such as 15 to 20 minutes, it will be effective. When agonal inspirations begin, intravenous transfusion improves cardiac activity only in some of the cases, while arterial blood transfusion gives good results both in the pre-agonal and agonal periods. It must be stressed, however, that in massive, noncompensated blood loss the effectiveness of intravenous as well as of intraarterial transfusion is directly dependent on the duration of hypotension and the stage of the terminal period. Thus, after 2 hours of hypotension the effectivenss of intravenous transfusion is less in the pre-agonal period and totally absent during agony. After 4 hours of hypotension intravenous blood transfusion in the pre-agonal stage results in a temporary

From the Laboratory of Experimental Physiology for Resuscitation of the Academy of Medical Sciences of the U.S.S.R., Moscow, Russia.

increase of cardiac activity. After prolonged hypotension intraarterial blood transfusion is more successful but also has its limits. Thus, after 4 hours of hypotension it gives good results during the pre-agonal period but is of little help during agony; after 5 hours of hypotension, even in the pre-agonal period, arterial blood transfusion gives only temporary improvement.[2]

Hence it follows that treatment with intraarterial blood transfusion should be started during the early stages of dying. Once the agonal period has set in, even when accompanied with rapid blood loss, intravenous jet injection of large quantities of blood, especially rapid transfusion, is not only useless but is often dangerous. Once the heart is acutely dilated by intravenous blood transfusion subsequent arterial transfusion of blood fails to give any effect. Consequently, if in severe shock or loss of blood intravenous transfusion of 250 to 500 ml. of blood fails to give a sustained rise of arterial blood pressure and fails to improve the cardiac output, intraarterial transfusion of blood must be resorted to immediately.

Yet, the effectiveness of arterial transfusion has its limits. It more often happens that the use of all the components of the combined resuscitation measures becomes necessary; though, in certain cases, for instance, in lethal loss of blood, arterial blood transfusion alone may be effective not only during the terminal period but even after the heart had stopped beating for a short time.

Artificial respiration represents the second indispensable element of the combined method of resuscitation. Artificial respiration should be started as early as possible, preferably simultaneously with the arterial transfusion, for it is essential to affect both the respiration and the cardiovascular system during resuscitation. Artificial respiration with the aid of an apparatus, besides ensuring good pulmonary ventilation, will, through reflex pathways, such as the Hering-Breuer reflex type, stimulate the respiratory center with impulses traveling from the lungs along the vagal fibers to the medullary centers. This stimulation can be effective only if blood circulation has already started in the medulla. The focus of stimulation under these conditions will spread from the medulla to the higher segments and the cortex of both hemispheres. The latter, with the restoration of its functions, provides the most perfect mechanism of controlling the functions of the body. There exists a direct relationship between the time required for the restoration of breathing and that for the restoration of the functions of the central nervous system. The first spontaneous inspiration points to the presence of a focus of stimulation in the medulla. The earlier it appears the earlier will the cerebral cortex return to life and the chance of resuscitation will be better. The interdependence between the degree of circulatory compensation and the possibility of respiratory restoration is seen, for instance, in the fact that such methods, like Laborde's, of neuroreflex influence on the respiratory center on the stimulation of the phrenic nerve by electric current are effective only when the arterial blood pressure is not lower than 80 to 100 mm. Hg. In clinical death the basic method of restoring respiration should be reflex stimulation of the respiratory center by dilatation of the lungs.

As artificial respiration with the aid of apparatus is now widely used, such questions as the composition of the gaseous mixture given to the patient and the analeptics used have acquired special importance. According to our data lobeline, cititone, or carbon dioxide cannot be compared to the reflex method for restoring respiration. Moreover, the deeper the depression to which the respiratory center is subjected the more dangerous is the use of analeptics, as they are capable of only a very brief restoration of respiratory activity and lead to rapid exhaustion and further depression of respiration. At the same time this lessens the possibilities of restoring respiration by other means. Pharmacologic stimulants are indicated only when the corneal reflexes are present and the arterial blood pressure is not below 60 mm. Hg. As to the composition of the gaseous mixture administered to the patient, we believe that the concentration of oxygen must not exceed 30 to 40 per cent. Prolonged administration of pure

oxygen or more than 40 per cent of oxygen during the terminal stage may lead to severe symptoms of hyperoxia. Addition of carbon dioxide (from 1.5 to 27 per cent) and the use of Carbogen (95 per cent oxygen plus 5 per cent carbon dioxide) under these conditions will not improve the situation.[3]

Cardiac defibrillation is the third element in the combined method of resuscitation. Fibrillation may supervene as a result of myocardial stimulation during hypoxia of any origin, during thoracic operations, during cardiac massage, and other measures for restoration of cardiac activity, during artificial hypothermia, and from electroshock. Pharmacologic defibrillation is giving place in recent years to the more effective electrical defibrillation.[4,5] The study of the mechanism of defibrillation has shown that it is conditioned rather by the usual stimulating action of electrical excitation than by the inhibitory action on the heart, as was formerly assumed. Our investigations in this field have shown that the most effective method of stopping fibrillation consists in applying to the heart a single electrical impulse of 0.01 second in duration, which is near to the time of useful myocardial stimulation. A special apparatus generates single electrical impulses in the form of a condenser discharge of a definite capacity (24 microfarads) with the inductance of the circuit of 0.25 henry. Fibrillation can be stopped with the aid of this apparatus either on the exposed heart or with the thorax intact.[6] If the fibrillation has lasted for more than 1 to 1½ minutes and also if it has supervened with insufficient or absent circulation or poor pulmonary ventilation, it is necessary to transfuse blood intraarterially or massage the heart directly and administer adequate artificial respiration prior to defibrillation.

Finally, the fourth and extremely important element of the combined therapy is direct, transthoracic massage of the heart. If the arterial transfusion of blood and artificial respiration used during the agonal period give no results and clinical death has supervened, massage of the heart should be started at once. Cardiac massage, for instance, often becomes necessary during anesthesia. Studies of terminal stages caused by overdosage of ether, pentothal sodium, and muscle relaxants were conducted at the laboratory. It was shown that during the early stages of dying with arrest of spontaneous respiration, and while cardiac activity is still retained, the main therapeutic measure consists of artificial respiration. As the cardiac activity weakens and the maximum arterial pressure falls below 60 mm. Hg, artificial respiration should be combined with intraarterial blood transfusion. When the cardiac activity ceases and clinical death occurs, the most effective measure consists in the direct massage of the heart combined with intraarterial blood transfusion and artificial respiration.

During cardiac massage it is essential to maintain the maximum blood pressure above 60 to 70 mm. Hg.[7] Our investigations have shown that this is best achieved through rhythmic compressions of the heart and fractional transfusions of aerated blood into the artery with epinephrine or norepinephrine added.

Though the causes of death are numerous, many phenomena accompanying the process of dying are to a great extent common to many types of extinction and restoration of vital functions.

The death of a living organism is the disintegration of its unity, interruption of interrelations of the organs and systems both with each other and the external environment. This discoordination develops first of all through suspension of activity of the higher areas of the central nervous system. As is known, the maximum time the cortical nervous cells can survive after blood circulation has ceased is 3 to 5 minutes. With longer periods, profound, usually irreversible changes take place.

Clinical death cannot be separated from the period of dying that precedes it. Sometimes this period can be so exhausting that the most important systems of the body perish before clinical death sets in. And, on the contrary, if the period of dying was sudden and short, resuscitation is still possible after 6 to 7 minutes from the beginning of clinical death.

It is quite natural that the investigators devoted much attention to the metabolic proc-

esses occurring during circulatory arrest. Biochemical research in our laboratory was mainly concerned with the oxidative processes in the body and the carbohydrate-phosphorus metabolism in the brain.[8,9]

Experiments on dogs have shown that at the very beginning of dying from blood loss, for instance, when the compensating mechanisms are still active, no profound metabolic changes take place. Definite changes may be detected only toward the end of the bleeding, when the animal has lost about half the total quantity of blood and the arterial pressure has fallen to 20 to 30 mm. Hg. Due to the great loss of blood and a decrease of the blood-flow velocity by almost 40 times, toward the end of bleeding the general consumption of oxygen by the body becomes insufficient and typical signs of hypoxic metabolism appear. The critical stage, as far as metabolism is concerned, is the terminal stage, i.e, the interval when regular breathing has ceased and the agonal state has not yet developed. Glycolysis, a more primitive form of metabolism begins to prevail in the brain tissue; catabolic phenomena prevail over the processes of synthesis. During agony, when physiologic functions are controlled by the bulbar centers only, a further increase of the glycolytic processes takes place. As a result of accumulation of a great quantity of underoxidized products of metabolism the condition of metabolic acidosis supervenes. Disruption of fat metabolism occurs at the same time. The intensity of glycolysis falls gradually as clinical death sets in. Its low level is incapable either of utilizing the sugar formed with the breakdown of glycogen or of demineralizing the inorganic phosphoric acid. The energy resources of the brain tissue are by now practically exhausted.

During the first minutes following the resumption of cardiac activity after 5 or 6 minutes of clinical death, the metabolic processes undergo no great changes. Two or 3 minutes after the resumption of circulation, aerobic glycolysis in the brain begins. With the resumption of breathing the energy resources of the brain tissue are gradually restored. It is interesting to note that the speed of circulation in the cerebral vessels during this period is considerably lower than in other organs. However, the cerebral tissue utilizes blood oxygen only to a negligible degree. Its return to oxidative metabolism during resuscitation takes place gradually. Only toward the end of the first hour after resuscitation does glycolysis disappear and the oxidative processes increase. At the same time oxygen deficiency of the cerebral tissues still continues, which is proved by the higher-than-normal level of lactic acid. The content of the underoxidized metabolites exceeds the initial level, whereas the alkaline reserves of the blood remain at a low level.

Complete normalization of the carbohydrate-phosphorus metabolism of the brain takes place approximately 72 hours after resuscitation. The hypoxic state continues until the functions of the cortex are more or less restored and the body is able to bring into play more efficient compensatory mechanisms.

As is seen from the above data, the biochemical changes in the cerebral tissue during clinical death are distinguished by their great mobility, the exhaustion of the energy reserves of the cells rapidly takes place, after which the destructive processes become irreversible.

The study of bioelectric phenomena in the cerebral cortex permitted detection of a number of important regularities. According to the electroencephalogram, even within 5 or 6 minutes of clinical death changes take place in the brain that make this period qualitatively heterogeneous. Thus, restoration of the electrical activity of the cortex after a short clinical death (1 to 3 minutes) differs from a prolonged one (4 or 5 minutes) though the average duration of dying is the same (15 minutes). The same phases of electroencephalographic restoration after a clinical death of long duration appear later than after a short clinical death. Besides, during the early stages of resuscitation after 4 or 5 minutes of clinical death there appears a special qualitatively distinctive form of activity in the form of spindle-shaped groups of sinusoidal oscillations, 7 to 14 per second, synchronous over the entire surface of the hemispheres and related to the rhythm of respiration.[10]

Morphologic investigations have made it possible to determine the character of changes in the brain following clinical death and revealed their evolution depending on the duration of life after hypoxia. The morphologic changes are directly related to the severity and duration of the period of dying and of clinical death.

The development of histopathologic changes in the brains of animals subjected to a 5-minute clinical death as a result of acute hemorrhage proceeds in several stages. Immediately after clinical death following a short dying period (7 to 10 minutes) and 20 to 30 minutes after resuscitation histopathologic changes are insignificant and are manifested as an acute swelling of separate cells. They are more pronounced when the period of dying is longer. Three hours after resuscitation, dispersion of the tigroid is noted. After 15 to 24 hours the intensity of the changes is accentuated: There is total tigrolysis and nuclear hyperchromatosis in a significant part of nerve cells, in some of them karyocytolysis occurs; astrocytes are swollen and drop their ramifications; perivascular edema is visible. Some 36 to 48 hours after resuscitation, certain signs of restoration are observed such as the tigroid again taking on stain. Yet, on the other hand, the pathologic process increases; protoplasma of certain cells becomes vacuolized, others stain darkly and decrease in size. On the seventh and the following days unchanged nerve cells are seen in all parts of the brain, but the changed ones are still plentiful. Of other changes vacuolization of the protoplasm, shrinkage, and karyocytolysis persist the longest. Only toward the thirtieth day of the animal's life after the experiment, the majority of cells regain their usual appearance. The longer the duration of clinical death or the dying period, the greater is the number of perishing cells and the number of minute areas of destruction in all regions of the brain, particularly in the cortex, in the cornu Ammonis, and in the cerebellum.[11]

The concept of high sensitivity of the central nervous system (especially of its brain cortex) to oxygen deficiency is generally accepted. However, one comes across cases, when in sustained circulatory insufficiency (blood loss, shock, etc.), with the arterial blood pressure level below 70 to 60 mm. Hg, the functions of the cortex of the brain are not significantly affected. Later on, despite restoration of the circulation, death will frequently occur. Here the deciding factor in the mechanism of death, when the replacement of blood comes too late, is cardiovascular insufficiency and insufficiency of the internal organs. Myocardial weakness in this case may prevail and then death occurs in a few hours from hemodynamic disorders or from hepatorenal insufficiency, in which case the organism dies somewhat later. What seems paradoxical is the fact that it is not the brain, the organ most vulnerable and sensitive to anoxia, that becomes the site of the most pronounced histopathologic changes. This, however, does not contradict the proposition of its high sensitivity to hypoxia. This property of the brain becomes manifest only when the whole body is placed in equal conditions of hypoxia, as, for instance, in acute anoxia or acute blood loss. In cases of gradual blood loss, hemorrhagic shock or prolonged hypotension a number of compensatory mechanisms protect the brain for some time from the noxious influence of the fall in blood pressure. Dilatation of the cerebral vessels and the increased utilization of oxygen from the arterial blood belong to this group of protective mechanisms. This concept of the mechanism of death in sustained hypotension dictates the necessity of a corresponding therapy, directed first of all at the normalization of the functions of the internal organs.

The above data and considerations, suggesting that in certain cases it is not the changes in the brain that determine the death of the body after sustained hypotension, do not remove the question of the role of the central mechanisms and the cerebral changes in the pathogenesis of blood loss.[12]

One of the most important and complicated problems with which the investigators of resuscitation are faced, is that of prolonging the duration of clinical death following which it would be possible to obtain complete and stable restoration of the vital functions. In

this connection it seemed most tempting to try to use artificial hypothermia and hibernation with the aim of inhibiting the destructive processes in the living tissues, which develop during the dying period and in clinical death.[13–16]

Artificial hypothermia (26 to 20°) obtained with the aid of general cooling and pentothal anesthesia enables one to obtain complete and sustained restoration of the vital functions in animals after clinical death has lasted up to 1 hour. With the aid of deep hypothermia (12 to 10°) we obtained recently complete and sustained restoration of the vital functions of the organism in animals after 2 hours' duration of clinical death.

At the same time it was shown that if the terminal state develops in the animals already hibernated or when hibernation is combined with hypothermia, the restoration of the vital functions becomes extremely difficult and, in a number of instances, fails. This may perhaps be explained by the fact that the lytic mixtures depress the nervous mechanisms of cardiovascular control and create an obstacle to the restoration of cardiac activity. The negative effect from the hibernation mixture is probably due to the fact that in the terminal stages, when the central and vegetative nervous systems are deeply inhibited, the lytic mixtures tend to depress them even more, which makes resuscitation extremely difficult.[17]

What has been said above justifies the conclusion that the leading factor, aiding survival of the higher sectors of the brain during hypoxia, is hypothermia and not hibernation. The latter, under experimental conditions when it was combined with hypothermia, made resuscitation difficult even after short terms of clinical death.

Further study of the physiopathology of death and resuscitation of the body must help to understand better the peculiarities of these extreme stages of life and make their treatment more successful.

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CLINICAL PROGRESS

Recent Trends in Therapy of Cerebral Vascular Disease

By SIGMUND N. GROCH, M.D., AND IRVING S. WRIGHT, M.D.

IN THE past decade great interest in the problems of cerebral vascular disease has developed. Increasing numbers of centers throughout the country have gained experience in the therapy of strokes, some of which offers considerable hope for the future.[1, 2] It is fitting at the close of this decade to review and assess what has been accomplished and ask what may we expect in the future.

Certain gaps in knowledge as well as definite variables are immediately obvious. Knowledge regarding the natural history of strokes is inadequate to assess fully the value of the therapeutic methods that have been advocated. In addition, the course of a stroke can be so variable from patient to patient that a large number of patients must be studied before any one given measure can be truly validated. All of us have seen many patients with stroke who appeared to be seriously ill at onset and who walked out of the hospital some weeks later, without "active" intervention on the part of the physician. Any disease with so inconsistant a picture must be most carefully investigated before final answers can be given.

From the Second (Cornell) Medical Service, Bellevue Hospital, New York City, and the Department of Medicine, Cornell University, College of Medicine, New York, New York.

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Conservative Therapy

It would appear that the attending physician's attitude toward his patient with stroke may play an imporant role in affecting the outcome. In a study of large numbers of patients with strokes, Nielsen[3] found that the mortality rate could be reduced from 44 to 31 per cent merely by improving the nature of the general medical care these patients received. In cerebral thrombosis the mortality rate was reduced from 30.2 to 24 per cent. Thus, one must adhere to the following precepts. One cannot be certain of the prognosis at onset. Coma, while carrying serious implications, need not end in death or serious residual impairment. Therefore, all patients with strokes should be made ambulatory and exercised as soon as possible. Maintenance of an adequate cardiac output must be assured. Close attention must be paid to insure adequate pulmonary ventilation. Dehydration must be avoided. Hypoglycemia should never occur and polycythemia must be corrected as rapidly as possible.

Unfortunately, even with the most expert medical and nursing care, there is an irreducible minimum beyond which conservative therapy cannot go, and for this reason more active intervention has been attempted.

Cerebral Thrombosis

Therapy has been aimed at three stages in the life history of cerebral thrombosis (1) in the prodromal stage when the individual may be experiencing recurrent transient episodes; (2) during the acute phase; (3) in the recovery phase and thereafter for a definite or indeterminate period of time.

Phase 1. The Period of Recurrent Transient Ischemic Episodes

The work of Kubik and Adams,[4] Fisher,[6] Denny-Brown,[7] and Millikan and associates[8, 9] has done much to clarify our concepts of the pathogenesis of transient ischemic attacks. It is clear that these episodes are far more common than was previously suspected. They may be evanescent, however, and must be inquired for most carefully during history taking. Fisher[10] found that of 125 patients with a diagnosis of cerebral thrombosis, 13 per cent had transient ischemic attacks as their only clinical manifestation of disease and 42 per cent had transient ischemic attacks progressing to persistent deficit. In a recent review of 57 patients with proved carotid artery occlusive disease, a history of transient ischemic episodes was obtained in 16 (25 per cent).[11]

A. Anticoagulant Therapy

In this variety of stroke, anticoagulant therapy has seemed to be quite efficacious. Dr. Millikan has been kind enough to allow us to give the most recent figures of the experience of the Mayo Clinic: in 163 patients with basilar artery insufficiency the use of anticoagulants has resulted in cessation of attacks in 148 patients. In patients with carotid artery insufficiency the attacks were stopped in 131 of 145 patients. Fisher[10] has reported a similar experience with anticoagulants: of 29 patients with transient ischemic attacks, anticoagulant therapy achieved cessation of recurrent attacks in 28. Upon cessation of anticoagulants in 20 of these patients transient ischemic attacks recurred in 12.

These figures are so impressive that they almost do away with the need for controlled studies. However, since we have found patients with transient ischemic attacks in whom the episodes ceased spontaneously[11] (as has Fisher),[10] a controlled study is considered desirable. At present a cooperative study of cerebral vascular disease is in progress at several institutions and perhaps an answer will be forthcoming. Certainly one can say that the evidence in favor of the efficacy of anticoagulant drugs in therapy of this variety of stroke is strongly suggestive.

B. Surgery

In recent years surgeons have attempted to aid individuals with transient ischemic attacks. They have had considerable success in lowering operative morbidity and mortality while re-establishing circulation in obstructed cervical internal carotid arteries and somewhat less success in obstructed vertebral arteries.[12, 13] In some patients surgery has succeeded in abolishing transient ischemic attacks when anticoagulant therapy has failed. The final answer is certainly in the future. We shall have to learn of the results of follow-up of patients and the results of additional groups. We know that our group has had a much higher morbidity and mortality in the performance of angiography,[14] which is an essential part of the diagnostic workup, and that some of the patients so treated at The New York Hospital and Bellevue Hospital to date have not done well. While there is no doubt that surgery has a place in the therapy of strokes, it may well be a more limited role than some workers at present suggest. Here again a controlled study would be of great value. A word of warning: a patient experiencing transient ischemic attacks need not have vascular disease. In the younger individual multiple sclerosis may certainly present in this fashion, and we have seen brain tumors cause just such a symptom complex.[15]

Phase 2. The Acute Phase

A. Carbon Dioxide Inhalation

Carbon dioxide is a most potent cerebral vasodilator. It is questionable, however, whether it can add any further vasodilator effect to an infarcted area. Two careful studies of the effects of carbon dioxide inhalation during the acute phase of a stroke have failed to find any benefit from it.[16, 17] In similar fashion, vasodilator drugs have not been found to be of value.[18–20]

B. Stellate Ganglion Block

There are numerous case reports in the literature describing spectacular results in individual patients following stellate block.

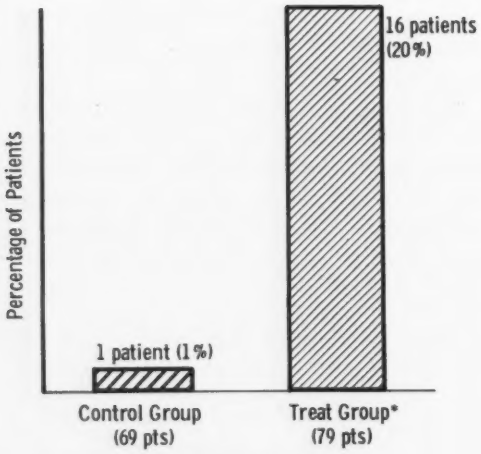

Figure 1

Incidence of hemorrhagic complications in untreated and treated patients.

De Takats reports that in a series of 55 patients, 55 per cent demonstrated improvement in their clinical status following single or multiple injections of the stellate ganglion.[21] It is difficult to see a physiologic basis for this, and in two controlled studies, no value of the procedure could be demonstrated.[17, 22] We find it even more difficult to ignore these controlled studies because of the variability of the picture of stroke.

C. Anticoagulant Therapy

There are several questions that must be asked as one contemplates the use of anticoagulant therapy in strokes:

1. What are the risks of misdiagnosis?
2. What is the rationale of such therapy?
3. What has been the risk of complications as experienced to date?
4. What has been the gain to date?

Answers. 1. There is a 10 per cent chance of diagnosing a small intracerebral hemorrhage as a cerebral thrombosis. The likelihood of overlooking some other type of cerebral lesion, such as subdural hematoma or brain tumor, is approximately 5 per cent.

2. Anticoagulants are used in the hope of preventing an extension of an intraluminal thrombosis and thus of limiting the area of infarction.[10] It is also hoped that, as in animals, anticoagulant therapy will hasten recanalization of the obstructed vessel.[23, 24] In addition, the work of Meyer[25] has demonstrated the prevention of sludging of blood in small cortical vessels with the use of anticoagulants. Finally, 14 per cent of the deaths in patients with cerebral thrombosis are due to pulmonary emboli and 37 per cent of all patients with a stroke have extracerebral thromboembolic complications with a mortality of 30 to 38 per cent.[1] Anticoagulant therapy may well prevent the occurrence of these complications or lessen their frequency.

3. If one should misdiagnose a small intracerebral hemorrhage as a cerebral thrombosis and initiate anticoagulant therapy, one obviously will worsen the situation. This would seem inevitable if a large enough group of patients is treated.

In addition, the raising of a prothrombin time above normal has risks inherent in the procedure itself. Several authors have now reported fatal cerebral hemorrhages in the course of anticoagulant therapy in the acute phase of cerebral thrombosis.[26-28] The protocols of these patients reveal that many of these complications have occurred in association with a prothrombin time well beyond the accepted therapeutic range. This does not absolve anticoagulant therapy, however, for this may occur with the best of laboratory control. The thromboplastin used by the authors reporting severe hemorrhagic complications has been a brain thromboplastin. Our group believes that this type of thromboplastin is not sufficiently sensitive for this type of work. In addition, our group believes that a dilution of plasma to 12.5 per cent is most helpful in detecting early excess in action on prothrombin activity before the undilute specimen rises into the dangerous area.[29]

It is our opinion that every patient should have a spinal fluid examination prior to the institution of anticoagulants for a stroke. Furthermore, we believe that to use anticoagulants

in the presence of severe hypertension is to court disaster.

In our controlled study we have not as yet had the ill fortune of a hemorrhagic complication resulting in death either in the acute phase or on long-term therapy. We hope that we can continue to avoid such a tragedy.

4. It is generally agreed that anticoagulant therapy is of no definite value if used after a complete lesion has occurred.[10, 17] In a slowly advancing stroke both Fisher[10] and Carter[17] report a definite benefit gained by the use of anticoagulants and this also has been our experience. On the other hand, others have reported anticoagulants to be of no benefit even in this type of stroke.[26] Here again it is hoped that the results of the Cooperative Study may be enlightening.

Anticoagulants have definitely been shown to reduce the incidence of extracerebral thrombosis if used during the acute phase of a stroke. In one large series the incidence has been reduced from 37 to 3 per cent.[30] It also has been the experience of our study group that this is true although at present the number of patients is not large enough to make definite statements.

Thus, one must balance the dangers of the use of anticoagulants against the benefits one hopes to gain. It would seem that at this point the answer is not available and one should avoid advocating the routine use of anticoagulants in the acute phase of a cerebral thrombosis. If the indivdual physician does use anticoagulants, he must carefully select his patients, realizing that this therapy is still in the early stages of development and that far more must be learned before all of the indications and contraindications are universally accepted.

D. Surgery

To date the good results claimed for surgery have occurred only if surgery has been undertaken for the treatment of transient ischemic attacks or very shortly (minutes) after a complete occlusion has taken place. The use of this procedure late in the development of a complete lesion has usually resulted in failure.[13, 31, 32] The successful areas approached have been the carotid arteries, especially at the bifurcation, and the vertebral arteries. Well-controlled long-term studies of the value of surgery for these conditions are needed.

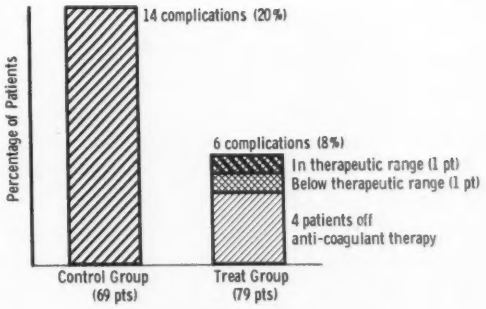

Figure 2

Incidence of thromboembolic complications in untreated and treated patients.

E. Fibrinolytic Agents

There are no large studies of the use of these agents in patients with strokes. It may well be that these agents will prove most efficacious in treatment of transient attacks or a slowly progressive stroke, the logic of such thinking being self-evident. It is hoped that a group that is planning to apply its resources to testing these agents will perform a controlled study of the effects of these drugs.

Phase 3. Recovery Phase

What are the facts known at present that support a study of long-term anticoagulant therapy following a complete or incomplete stroke? In a recent paper the recurrence rate of strokes in a large number of patients was described.[33] At the end of 1 year one third of the survivors of the acute phase had had another stroke. By the end of 4 years, two thirds of the initial surviving patients had experienced a second stroke. Eighty-two per cent of all the deaths in the group surviving the initial stroke were due to cerebral or coronary artery disease. These figures are shocking in their indictment of atherosclerosis with resulting thromboembolism as the cause of repetitive disability and death in this particular group of patients.

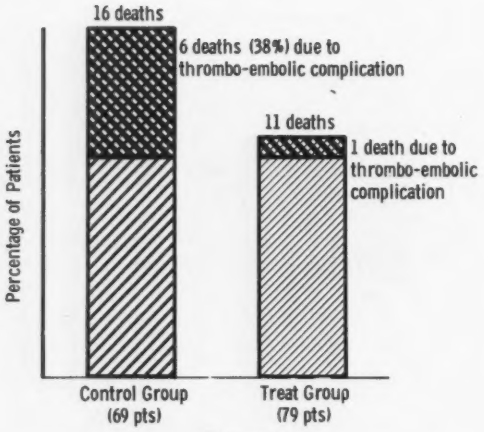

Figure 3

Mortality rate in untreated and treated patients.

In another study, the greatest cause of death was again disease of the vessels of the brain and heart.[34] In yet another study of 65 patients with thrombosis of the carotid-middle cerebral tree, 34 per cent were dead of recurrent stroke in 2 years.[35]

Thus, one would use anticoagulants in an attempt to reduce the incidence of recurrent thrombosis.

Is there a risk to long-term anticoagulant therapy. In our study there has been a 20 per cent incidence of nonfatal hemorrhagic complications, some of which were definitely serious, with one patient experiencing a subarachnoid hemorrhage (fig. 1).

In other studies of the long-term use of anticoagulant drugs in the therapy of coronary artery disease bleeding complications have occurred with a similar incidence.[36] In addition, fatal intracerebral hemorrhage has occurred in 3 per cent of patients treated.[37]

What has been the gain reported? McDevitt and associates[38] recently described their experience with a small group of patients who were allowed to serve as their own controls during periods when anticoagulant therapy was discontinued. Of 28 patients, 21 patients experienced a recurrence while off anticoagulant therapy, whereas 8 experienced a recurrence while on anticoagulant therapy.

In our controlled study the number of patients is not large enough to attain any degree of significance (148 patients followed for a maximum period of 33 months). However, there has been a reduction in the incidence of thromboembolism (20 versus 8 per cent) and in the number of deaths attributable to recurrent thromboembolism (38 versus 9 per cent). In addition some of the complications in the "anticoagulant group" occurred after therapy had been discontinued (figs. 2 and 3). Thus, the results are suggestive of benefit to be derived from long-term therapy.

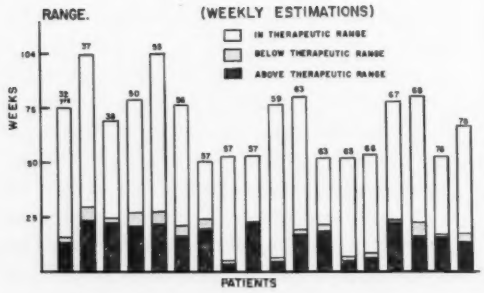

Figure 4

Deviations of prothrombin time from therapeutic range in long-term patients.

A last word about one of the problems of long-term anticoagulant therapy. The charts of a group of patients who had received anticoagulant therapy for 12 months or more were reviewed (fig. 4). They demonstrated the difficulty of maintaining a patient within therapeutic range for any prolonged period of time. One cannot therefore assume that adequate protection against recurrent thromboembolism exists at all times. This emphasizes the desirability of close supervision by the physician.

Cerebral Embolism

The value of long-term anticoagulant therapy in the prevention of recurrent cerebral and peripheral embolism appears to be well established.[39] However, the early use of anticoagulants in patients with a clinical diagnosis of cerebral embolus has been questioned. Blumgart and associates have demonstrated that with the early use of anticoagulants in acute myocardial infarction there is no increase in myocardial hemorrhage.[40] Animal

experiments performed by two groups of researchers indicate, however, that the early use of anticoagulants in cerebral vascular disease tends to increase the degree of hemorrhage in hemorrhagic infarcts.[41, 42]

Since more than a majority of infarcts produced by cerebral emboli are hemorrhagic, one must wonder how early one may use anticoagulants with impunity.[43, 44] There are two studies of the use of anticoagulants in the acute phase of a cerebral embolus in man. Wells,[45] in a review of a series of records from The New York Hospital, found a mortality rate of 25 per cent of 53 patients who did not receive anticoagulant therapy. Contrasted with this result is a 6 per cent mortality of 34 patients who did receive anticoagulant therapy. Although these numbers are small, they do indicate that anticoagulants did not worsen the prognosis in this group of patients. It should be pointed out, however, that although the patients who did not receive anticoagulants had clear and colorless cerebrospinal fluids, five patients who received anticoagulants shortly after the acute stroke or who were receiving anticoagulants at the time of the stroke, had an appreciable number of red blood cells in the cerebrospinal fluid. These patients either died or survived with a severe disability.

Carter[46] has reported a small number of patients who received anticoagulant therapy shortly after a diagnosis of cerebral embolism. In this study there also was a difference of mortality rates, 24 per cent in the treated group and 54 per cent in the control group. In addition, autopsies were performed on seven patients who died after receiving anticoagulants. In none did he observe any increase in cerebral hemorrhage.

How then does one balance the therapy of early recurrent embolus with the above observations? Probably it is best to compromise. We usually withhold anticoagulants for a period of 24 to 36 hours after an acute cerebral embolus. In addition, anticoagulants are not administered in the presence of a xanthochromic cerebral spinal fluid.

Cerebral Hemorrhage

Unfortunately, there is little that we can do or discuss concerning intracerebral hemorrhage. The prognosis is poor for the massive hemorrhage with the exception of those few patients in whom neurosurgical evacuation of an intracerebral hematoma produces spectacular improvement. We have not reached a point where we can prevent an intracerebral hemorrhage and we can do little for the acute phase. All one can say is that for prophylaxis, severe hypertension with recurrent headache should be treated vigorously.

Subarachnoid hemorrhage has a better prognosis when treated by suitable surgical procedures.

Summary

The various measures available for the therapy of a patient with a stroke have been discussed. The value of vigorous conservative therapy has been emphasized. The role of anticoagulant drugs has been detailed. This mode of therapy seems most efficacious in treatment of recurrent transient ischemic attacks and the slowly progressive stroke. The value of anticoagulants in the acute phase of cerebral thrombosis and in long-term postinfarction therapy is not clear as yet. The role of anticoagulant drugs in treatment of cerebral embolism seems well established. It may be wise to delay institution of these drugs for 24 to 36 hours after the acute stroke. Surgical procedures give promise of value in certain well-defined syndromes. The patient with cerebral hemorrhage remains a formidable therapeutic problem.

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I believe there shall never be an Anarchy in Heaven; but, as there are Hierarchies amongst the Angels, so shall there be degrees of priority amongst the Saints. Yet is it (I protest) beyond my ambition to aspire unto the first ranks; my desires only are (and I shall be happy therein) to be but the last man, and bring up the Rere in Heaven. —Sir Thomas Browne. *Religio Medici.* Edited by W. A. Greenhill, M.D. London, Macmillan and Co., Ltd., 1950, p. 89.

ABSTRACTS

ATHEROSCLEROSIS

Barrow, J. G., Quinlan, C. B., Cooper, G. R., Whitner, V. S., and Goodloe, M. H. R.: Studies in Atherosclerosis. III. An Epidemiologic Study of Atherosclerosis in Trappist and Benedictine Monks: A Preliminary Report. Ann. Int. Med. 52: 368 (Feb.), 1960.

The outline of a prolonged longitudinal epidemiologic study of atherosclerosis in 2 unique population groups is presented. An analysis of the diet reveals that the 2 groups differ in their dietary habits. One group, the lacto-ovo-vegetarian Trappist group, derive 26 per cent of their total calories from fat, and 43 per cent of their fat is of animal origin. The other group, a Benedictine community, derive 45 per cent of their total calories from fat and 75 per cent of this fat is of animal origin. The Trappist group appears to have significantly lower levels of most serum lipid constituents, but on an individual basis, serum lipids cannot be correlated with fat intake alone. It is concluded, on the basis of the preliminary report, that most serum lipids vary on a group basis with age and dietary fat intake, but that on an individual basis there appear to be factors other than age and dietary fat that affect serum lipids.

KAYDEN

Day, A. J.: Removal of Cholesterol from Reticulo-Endothelial Cells. Brit. J. Exper. Path. 41: 112 (Apr.), 1960.

Suspensions of cholesterol and of various cholesteryl esters were injected intraperitoneally into male albino rats and the uptake of these substances in the sternal lymph nodes and their subsequent removal was observed. Almost all of the cholesterol which was taken up was removed from the nodes within 10 days, but there was no difference in the rate of removal of cholesterol with the different preparations. Cholesterol emulsified in corn oil appeared to be removed more rapidly initially than the other preparations. The ingestion of unesterified cholesterol by the nodes was followed by an increase in the ester, while the ingestion of cholesteryl esters was followed by an increase in free cholesterol. The uptake of both cholesterol and cholesteryl oleate resulted in the accumulation of phospholipids and total fatty acids in the lymph nodes. These substances may be derived from the blood or lymph. It was considered that these metabolic changes may influence the removal of cholesterol from reticuloendothelial cells.

KALMANSOHN

Hamilton, R. E., and Pilgeram, L. O.: Lipid Bound Glutamic Acid Deficiency in Aging Arteriosclerotic Subjects. Proc. Soc. Exper. Biol. & Med. 103: 574 (Mar.), 1960.

This study demonstrates that the lipid-bound, ninhydrin-positive constituent identified as glutamic acid is present as a constituent of human plasma. The lipid factor is deficient in the aged, arteriosclerotic human subject; these individuals have about half the "normal" average plasma concentration. The change in distribution ratio of glumatic acid between alpha and beta lipoprotein fractions favors the beta fraction and appears to be a part of a defective mechanism for metabo-

lism of these lipoprotein moieties. The normal subject has 47 per cent in the alpha fraction compared to 35 per cent in this fraction for the arteriosclerotic patient. This deficiency of lipid-bound glutamic acid may be related to a defective blood coagulation system in the human arteriosclerotic individual.

KRAUSE

Hashim, S. A., Arteaga, A., and Van Itallie, T. B.: Effect of a Saturated Medium-chain Triglyceride on Serum-lipids in Man. Lancet 1: 1105 (May 21), 1960.

A synthetic fat, medium-chain triglyceride (MCT) was used as the sole source of dietary fat in formula feeding experiments on human subjects. It is almost devoid of linoleic acid. The serum-lipid responses obtained with MCT were compared with those obtained when corn oil or butter was substituted in the formula diet in isocaloric amounts. Whenever a subject's regime was changed from an ad-libitum hospital diet to a formula diet, serum lipids fell regardless of the type of fat in the formula. When MCT was substituted for corn oil, serum lipids rose transiently to a significant extent and then returned to only a slight elevation. When compared with butter, serum lipids increased appreciably when butter followed MCT and decreased appreciably when MCT followed butter. Thus, the cholesterol raising properties of butter cannot be ascribed to medium-chain triglycerides nor the cholesterol lowering properties of MCT to linoleic acid. The results of the study are most consistent with the hypothesis that the effect of a dietary fat on serum-cholesterol can be related to certain of its physical characteristics such as melting point or miscibility with water.

KURLAND

Schwenk, E., and Stevens, D. F.: Deposition of Cholesterol in Experimental Rabbit Atherosclerosis. Proc. Soc. Exper. Biol. & Med. 103: 614 (Mar.), 1960.

The experiments here reported are in agreement with the data of previous investigators who have established that exogenous cholesterol is deposited in tissues. This work, in addition, demonstrates that cholesterol, once deposited, is constantly exchanged between tissues including aorta and blood, and that the amount involved in these shifts is extremely small. The minute amount of the deposit in the aorta—only 1/3000 of 1 per cent of the administered cholesterol—may explain why the accumulation of deposits in the aorta is so slow and supports the concept that cholesterol deposition is not the primary damaging factor in atherosclerosis.

KRAUSE

Shafrir, E., and Steinberg, D.: The Essential Role of the Adrenal Cortex in the Response of Plasma Free Fatty Acids, Cholesterol, and Phospholipids to Epinephrine Injection. J. Clin. Invest. 39: 310 (Feb.), 1960.

These studies were carried out in dogs and were designed to study the role of the pituitary-adrenal axis in conditioning the lipid responses to epinephrine. In normal dogs intravenous injections of aqueous epinephrine (20 to 25 μg. per Kg.) caused an elevation of plasma-free fatty acid (FFA) maximal at 5 to 10 minutes and returning to normal at about 20 minutes. After adrenalectomy or hypophysectomy the same dogs, given the same doses of epinephrine, failed to show any elevation of plasma FFA. Treatment with cortisone, however, completely restored the FFA responses to levels similar to those seen preoperatively. In normal dogs subcutaneous injections of epinephrine in oil (0.6 μg. per Kg.) caused an elevation of plasma FFA at 2 to 3 hours and returning to normal levels at about 6 hours. Twenty-four hours later plasma cholesterol and phospholipid levels were significantly elevated. After adrenalectomy or hypophysectomy the FFA, cholesterol and phospholipid responses to injections of epinephrine in oil were abolished completely or reduced to very low levels. Treatment of adrenalectomized dogs with cortisone restored the FFA, cholesterol, and phospholipid responses to levels comparable with those seen preoperatively. Treatment of hypophysectomized dogs with cortisone fully restored the FFA responses to epinephrine; treatment with adrenotrophic hormone partially restored the FFA response and completely restored the cholesterol and phospholipid responses to epinephrine. Administration of cortisone to normal dogs considerably potentiated the plasma FFA response to injected epinephrine, elevated levels persisting up to 24 hours. It is suggested that the mobilization of FFA and of lipoproteins by epinephrine is dependent upon intact adrenal function and in particular on the simultaneous availability of cortisone or cortisone-like steroids.

KAYDEN

Taylor, C. B., Patton, D., Yogi, N., and Cox, G. B.: Diet as a Source of Serum Cholesterol in Man. Proc. Soc. Exper. Biol. & Med. 103: 768, (Apr.), 1960.

The purpose of this study was to determine what proportion of serum cholesterol normally can arise from synthesis by liver tissue and how much from synthesis by extrahepatic tissues. On the hypothesis that by feeding a cholesterol-rich diet, the liver would be suppressed and thereby eliminated as a source of serum cholesterol, the authors labeled dietary cholesterol with Carbon^{14}

so that they could determine the contribution of dietary cholesterol to serum cholesterol. A specially prepared diet of labeled and unlabeled cholesterol was fed to healthy adults for 8 weeks. One group of 4 subjects ingested a daily dose of 10 grams of egg yolk containing 1 gram of C^{14} cholesterol. In the other group, 7 subjects each consumed a daily dose of 20 grams of egg yolk containing 4 grams of C^{14} cholesterol. In group I (4 subjects) the diet was the source of 24 per cent of the serum cholesterol. Presumably then, the balance was coming from extrahepatic tissues or residual unsuppressed hepatic cholesterol synthesis. In group II (7 subjects) the diet supplied 31 per cent of the serum cholesterol and the remaining 69 per cent was believed to represent the contribution of extrahepatic tissues if hepatic cholesterol in man was suppressible by dietary cholesterol. In both groups serum cholesterol reached its peak in 4 to 5 weeks and remained constant to the end of the 8-week period. Presumably, then, at least 3/4 of the serum cholesterol of these subjects in the experiment was derived from cholesterol synthesis in extrahepatic tissues.

KRAUSE

Tupeinen, O., Roine, P., Pekkarinen, M., Karvonen, M. J., Rautanen, Y., Runeberg, J., and Alivirta, P.: Effect on Serum-cholesterol Level of Replacement of Dietary Milk Fat by Soybean Oil. Lancet 1: 196 (Jan. 23), 1960.

A study was undertaken to ascertain whether it was possible to devise dietary changes which would be acceptable in the long run and which would decrease serum cholesterol. Two mental hospitals were studied. In 1 of these dietary changes were instituted, replacing the milk fat in the original diet with vegetable oils mainly soybean oil and replacing butter and margarine with special unsaturated margarines. The other hospital served as a control group. Serum cholesterol decreased significantly in the experimental population but did not change in the control group. The higher the initial cholesterol, the greater its decrease. It is hoped to obtain subsequent data on the effect of these changes on the development of atherosclerosis.

KURLAND

BLOOD COAGULATION AND THROMBOEMBOLISM

Boyles, P. W.: Thrombolysis in Dogs with Human Fibrinolysin. J. Lab. & Clin. Med. 54: 551 (Oct.), 1959.

The effectiveness of human fibrinolysin was studied on induced radiopaque thrombi in partially occluded dog veins. Segmental radiopaque clots were produced by entrapment of radiopaque material in an induced blood clot. The thrombi were produced with brain thromboplastin, which was shown to be free of both fibrinolysin and profibrinolysin. Human fibrinolysin was injected intravenously 1 hour after formation of the clot. Serial x-rays were taken in treated and in control animals. Prothrombin and fibrinogen values were also determined. Serial observations both by x-ray and biochemical determinations showed human fibrinolysin to be an effective in vivo thrombolytic agent. There were no apparent alterations in various coagulation factors in the presence of increasing lysis of radiopaque blood clots and decreasing levels of circulating fibrinogen.

MAXWELL

Darby, J. P., Jr., Sorensen, R. J., O'Brien, T. F., and Teschan, P. E.: Efficient Heparin Assay for Monitoring Regional Heparinization and Hemodialysis. New England J. Med. 262: 658 (Mar. 31), 1960.

The authors modified the regional heparinization procedure of the extracorporeal dialyzer circuit in artificial-kidney hemodialysis. They further employed a more sensitive and rapid means of heparin assay during dialysis. These methods were applied in 17 dialyses in 3 patients. The results proved to be simple, practical, and effective thus warranting their more general use in the field of artificial kidney hemodialysis.

SAGALL

Feruglio, G., Sandberg, H., and Bellet, S.: Postoperative Changes in Blood Coagulation in Elderly Patients. Am. J. Cardiol. 5: 477 (Apr.), 1960.

Coagulation studies were performed in 15 patients aged 67 to 93 immediately before and on the third and seventh days after surgery. Of the 13 patients undergoing major surgery, nearly all showed on the third postoperative day a hypocoagulable state as indicated by a prolonged coagulation time, decreased platelet count, and lessened heparin tolerance. However, thromboplastin activity at this time was increased as demonstrated by a reduced recalcification time. On the seventh postoperative day nearly all patients were in a hypercoagulable state as shown by all 4 tests, and this state was thought to have been a consequence of tissue injury. The degree of hypercoagulability was greater than that found in younger patients under similar circumstances and was considered to be of possible importance in producing the greater incidence of postoperative thromboembolic disease in elderly individuals. In

the 2 patients having minor surgery no significant coagulation change was found postoperatively. Prothrombin activity and residual prothrombin measurements in the 15 patients showed no consistent trends after surgery.

ROGERS

Fragge, R. G., Bernstein, I. L., and Bell, J.: Fatal "Waterhouse-Friderichsen Syndrome" due to Dicumarol. Ann. Int. Med. **52**: 923 (Apirl), 1960.

Four documented cases of bilateral adrenal hemorrhage incident to anticoagulant therapy have been previously reported. Three of the patients had received heparin and I Dicumarol. In the Dicumarol-treated patient emboli and infarctions were discovered in other organs and hence adrenal infarction could not conclusively be proved as the primary cause of hemorrhage. The authors review the common causes of adrenal hemorrhage and the clinical diagnosis of the entity. The patient reported displayed a marked idiosyncrasy to Dicumarol, wherin 550 mg. administered over a 3-day interval lowered the prothrombin time to 10 per cent of the control value (or 45 seconds) on the fifth day. No other cause for death except bilateral adrenal hemorrhage was found at autopsy.

KRAUSE

Gibbs, N. M.: The Prophylaxis of Pulmonary Embolism. Brit. J. Surg. **47**: 282 (Nov.), 1959.

Lower limb thrombosis occurs at 2 main sites: the leg and the thigh. The author points out that thrombosis in the leg is most common in the intramuscular veins of the soleus muscle. This is due to wear and tear inflicted upon the veins as a result of the soleus muscle's venous pump action. These veins undergo progressive distortion and dilatation with advancing age. Thrombosis in the thigh occurs near the inguinal ligament, where many large veins meet, creating a potential area for stasis. Stasis in the leg veins will aggravate thigh vein stasis. Methods for preventing thrombosis in the postoperative patient have proved ineffective in most cases. A clinical program for the prevention of thrombosis by exercise of the soleus muscle is outlined. The "soleus ergometer" is described. This consists of a vertically mounted, rubber-padded platform, with a curved heel support. By means of spring tension, the platform is pivoted at the base and rotates through an angle of 25° on plantar flexion. An attached meter detects correct use of the platform by the patient. The best method for prevention of thigh vein stasis is frequent change of position.

MAXWELL

Holger-Madsen, T., and Schioler, M.: Increased Heparin Resistance after Operation Measured by the Plasma Heparin Thrombin Time. Acta chir. scandinav. **118**: 257, 1960.

Postoperative increase in heparin resistance has been previously demonstrated by the heparin tolerance test. Twenty patients were investigated after various surgical procedures to ascertain whether a postoperative increase in heparin tolerance might be demonstrated by the plasma-heparin-thrombin time. In this test, heparin is added to platelet-poor plasma and the clotting time with thrombin is determined. The patients who underwent abdominal surgery all had a normal preoperative heparin-thrombin time and all but 1 had a normal heparin clotting time. In all these patients a distinct postoperative increase in the heparin resistance was reflected in both tests usually by the first or second postoperative day and was maximal between the third and sixth day. Most of the thoracic surgery cases had shorter heparin-thrombin and heparin clotting times before operation. In all patients there was a further increase in heparin resistance after operation.

KURLAND

Hutchison, H. E., Stark, J. M., and Chapman, J. A.: Platelet Serotonin and Normal Haemostasis. J. Clin. Path. **12**: 265 (May), 1959.

Serotonin (5-hydroxytryptamine) is thought to be a vasoconstrictor; however, its physiologic function has not been established. It is known to be carried in the blood by platelets, and investigators have frequently suggested that serotonin takes part in hemostasis. Recent evidence has shown that platelets can be deprived of serotonin by the action of active alkaloids of *Rauwolfia serpentina*. In addition, platelets lose their ability to take up any further serotonin. Despite this action, no overt hemorrhagic tendencies develop. The homestatic mechanism of serotonin has been studied extensively by recent investigators, in patients receiving reserpine; however, no demonstrable abnormality was found. The present study was carried out in 12 manic-depressive patients who were receiving reserpine. Control observations were made on 6 of them 6 weeks prior to the institution of reserpine therapy. Measurements of bleeding time, silicone clotting time, platelet count, prothrombin time, consumption index and the thromboplastin generation were performed. In addition, platelet serotonin content, plasma clot retraction, and capillary response to injury were measured. Results indicated no demonstrable defect in any of the tested hemostatic mechanisms.

MAXWELL

Hyun, B. H., Dawson, E. A., Butcher, J., and Custer, R. P.: Studies on Soybean Phosphatide (Inosithin) as a Platelet Substitute. Stability and Effective Concentrations in the Thromboplastin Generation Test. Am. J. Clin. Path. 33: 209 (Mar.), 1960.

In this article the thromboplastin generation test has been used to measure the optimal range of effective concentrations of Inosithin in vitro systems. Inosithin is a phosphatide derived from soybeans and was found to be a reliable substitute for human platelets in the thromboplastin generation test. It may even be more sensitive than human platelets in detecting mild degrees of hemorrhagic disease owing to deficient plasma and serum factors. Inosithin was found to be resistant to cold, heat, and storage.

KAYDEN

Marshall, J., and Shaw, D. A.: Anticoagulant Therapy in Acute Cerebrovascular Accidents. Lancet 1: 995 (May 7), 1960.

A trial was planned to assess the influence of anticoagulant therapy on the immediate mortality of acute cerebrovascular accident of recent onset. All patients were submitted to cerebral angiography. All patients were under 70 years of age. They had sustained in the 72 hours before admission severe and persistent disturbances of brain function thought to be due to an acute cerebrovascular lesion other than hemorrhage, hematoma, or aneurysm. No source of embolism was apparent. Cases were randomized in pairs. Those in the treatment group were started on heparin and continued on phenindione after 2 days. Prothrombin times were maintained at 2 to 3 times the control values. Twenty-six patients were treated with anticoagulants of whom 20 survived to 6 weeks; 25 patients were in the control group of whom 22 survived to 6 weeks. No benefit from anticoagulant treatment was shown.

KURLAND

Miale, J. B., and Winningham, A. R.: A True Micromethod for Prothrombin Time, Using Capillary Blood and Disposable Multipurpose Micropipet. Am. J. Clin. Path. 33: 214 (Mar.), 1960.

The authors describe a new micromethod for determining the prothrombin time of oxalated plasma. Capillary blood was collected with a disposable micropipette and mixed with a measured amount of oxalate. The micropipettes were centrifuged and the packed red blood cells discarded. A measured amount of oxalated plasma was blown from the micropipette into a test tube and the prothrombin time determined by clotting of the thromboplastin—calcium chloride plasma mixture. Reproducibility of the method was very good and comparable with that obtained on venous blood. The prothrombin times obtained by the micromethod were compared with those obtained with venous blood in the 1-stage test in 25 normal and 65 abnormal subjects. There was an excellent statistical correlation between the 2 methods. It is suggested that this method can be substituted for the standard 1-stage test of prothrombin time using venous blood.

KAYDEN

Poller, L.: Factor VII and Heparin in Thrombosis. J. Clin. Path. 12: 331 (July), 1959.

It has been shown that factor VII, the accelerator complex of prothrombin conversion present in both plasma and serum, is reduced by treatment with drugs of the dicoumarin group. In patients with recent thromboembolic disease, it has been shown that the anticoagulant action of heparin on plasma clotting times has been significantly reduced and furthermore that there was a rise in plasma factor VII activity in such patients at the same stage of their illness. The determination of the association, if any, between the increase in factor VII activity and the "heparin resistance" of these cases was the aim of this study. The results indicate that the clotting time is markedly shortened by the addition of factor VII solution, and, in fact, with increasing volumes of factor VII, the anticoagulant effect of heparin may be completely neutralized in vitro. The antiheparin activity of factor VII may be due to other serum factors adsorbed upon it. These include factor IX and possibly factor X. The demonstration of marked antagonism between factor VII and heparin may be explained by 2 theories of the possible relationship to thrombosis. The first is that increased factor VII activity may be a causative agent in the production of thrombosis, neutralizing the natural anticoagulant, heparin, and upsetting the balance of coagulation. The second possible explanation is that the increased factor VII activity results from serum factors released into the circulation from the thrombus. This demonstration of the neutralization of the natural anticoagulant by factor VII provides a firm basis for the administration of the dicoumarin-type drugs in these conditions in which the main function is to depress the raised level of factor VII activity.

MAXWELL

Sacker, L. S., Saunders, K. E., Page, B., and Goodfellow, M.: Dilithium Sequestrene as an Anticoagulant. J. Clin. Path. 12: 254 (May), 1959.

Many anticoagulants have been used in the past

for blood specimens; however, because most have contained sodium or potassium salts, they have been unsuitable for sodium or potassium determination by flame photometry. Calcium heparin was for many years the only suitable anticoagulant for such determination, but it is very expensive. In the past few years disodium sequestrene and dipotassium sequestrene have been introduced for routine hematologic studies because of their superior effect in preserving the morphology of leukocytes and preventing the clumping of platelets. Dilithium sequestrene was prepared and its properties were studied as an anticoagulant. It was found to have the same hematologic preserving properties as the disodium and dipotassium salts, but in addition the specimens of blood could be used for sodium and potassium determinations. However, previous studies had indicated that dilithium sequestrene was unsatisfactory because of its low solubility. On the other hand, results of the present study show dilithium to have the same solubility as the disodium and dipotassium salts under similar conditions. Moreover, chemical determinations, such as sodium, potassium, chloride, bicarbonate, urea, phosphatase, cholesterol, and bilirubin, as well as routine hematologic studies, yielded the same results as when disodium or dipotassium sequestrene or calcium heparin was employed as an anticoagulant.

MAXWELL

Wessler, S., and Reimer, S. M.: The Role of Human Coagulation Factors in Serum-Induced Thrombosis. J. Clin. Invest. **39**: 262 (Feb.), 1960.

The authors have previously described an in vivo method for studying the influence of specific coagulation factors on the formation of thrombi. The systemic infusion of serum into rabbits will rapidly induce thrombosis in vascular segments containing stagnant blood far removed from the site of infusion. The activity in serum responsible for thrombosis arises during coagulation and is not species-specific. The phenomenon of in vivo thrombosis is quantitatively related to the amount of serum infused and forms the basis of a bioassay for measuring the serum thrombotic accelerator (STA) activity of normal human serum. The STA activity of normal human sera was compared with that of sera obtained from patients with known heredofamilial coagulation defects. Normal STA activity was found in sera from patients deficient in factor V, factor VII, factor VIII, or factor X. Sera from patients deficient in factor IX or Hageman factor were essentially devoid of STA activity. Sera from patients deficient in plasma thromboplastin antecedent had a significantly less than normal but a measurable quantity of STA activity.

KAYDEN

CONGENITAL ANOMALIES

Giraud, G., Latour, H., Puech, P., and Olivier, G.: Persistence of a Common Atrio-ventricular Canal. II. New Diagnostic Elements. Arch. mal. coeur. **53**: 48 (Jan.), 1960.

Of 21 patients with persistent common atrioventricular canal, confirmed by autopsy or cardiac catheterization, the frontal QRS axis of the electrocardiogram was situated between —60° and —110° in 14; these patients showed complete as well as partial persistence, but only slight increase in right ventricular pressure. The frontal QRS axis was situated between —135° and —160° in 3 patients, all of whom had marked right ventricular hypertension, caused by associated pulmonary stenosis or hypertension. The axis was situated between —30° and —60° in 4 patients, of whom 2 had complete persistence and 2 marked levoposition of the defect, leading to right ventricular hypoplasia. Incomplete right bundle-branch block was present in V_1 in all patients; it was isolated in most of the patients with partial defects, and accompanied by signs suggestive of left ventricular hypertrophy in most of the complete defects. A pronounced left hypertrophy pattern was seen only in levoposition of the defect leading to right ventricular hypoplasia. A marked right ventricular hypertrophy pattern was seen only in pulmonary hypertension or stenosis or in marked dextroposition of the defect. Insufficiency of the mitral and tricuspid values characteristic of the defect can be only rarely demonstrated by registration of a regurgitation wave during catheterization of the right atrium or in pulmonary capillary pressure curves. Usually the curves even in the immediate vicinity of the valves are normal, and diagnosis can be made only by repeated passage of the catheter through the valves in and out of the ventricle. During the passage of normal valves the catheter registers a sharp return of the systolic peak to the base line during the T-wave, whereas during passage of insufficient valves the return is gradual or is followed by a secondary ascent.

LEPESCHKIN

Holt, M., and Oram, S.: Familial Heart Disease with Skeletal Malformations. Brit. Heart J. **22**: 236 (Apr.), 1960.

Details are given of a family in which members of 4 generations were affected by both congenital heart disease and skeletal anomalies. The malformation was of a similar type in all the affected members; the congenital heart disease was manifested by atrial septal defects with bizarre arrhythmias and the skeletal defects by anomalies of the hands. The inheritance was of the Mendelian dominant type.

KALMANSOHN

Vela, J. E., Martinez, C .G., Ginefra, P., Portillo, B., Echevarria, M. V., Pileggi, F., and Correa, R.: Contribution to the Study of Dextrocardia. Analysis of 36 Cases. Arch. Inst. Cardiol. de México. **30:** 1 (Jan.-Feb.), 1960.

A clinical, radiologic, and electrocardiographic study of 36 cases of dextrocardia is presented. Any abnormal position of the heart in the right side of the chest was included. Congenital dextrocardias may or may not be associated with transposition of the abdominal viscera. The former group should be subdivided into those with universal inversion of the viscera and of the cardiac chambers and those with transposition of the abdominal viscera and the atria. This latter group is related to corrected transposition of the great vessels with levocardia. Dextrocardia in the absence of transposition of abdominal viscera may or may not be associated to transposition of the cardiac chambers. Diagnosis is discussed on the basis of clinical, radiologic, and electrocardiographic data.

BRACHFELD

CONGESTIVE HEART FAILURE

Hammond, J. D. S., and Ross, R. S.: The Proteins of Serum and Oedema Fluid in Heart Failure Studied by Paper Electrophoresis. Clin. Sc. **19:** 119, 1960.

The role of alterations in the colloid osmotic pressure of the plasma and of increased capillary permeability with a subsequent rise in the interstitial colloid osmotic pressure requires clarification. In the present study, accurate determinations were made of total protein concentrations of simultaneously collected samples of serum and edema fluid from a group of patients with heart failure. The total serum protein concentration was reduced below normal in 5 of the 11 patients, and the mean value was significantly lower than normal. In 9 patients the albumin percentage and concentration were decreased and in 8 patients the total serum globulin concentration was elevated. Every specimen of edema fluid contained albumin and all the electrophoretic globulin fractions of the serum. The total protein concentration of the edema fluid was always much less than that of the serum, the mean being 4.3 mg. per ml. The albumin in edema fluid formed a larger fraction of the total protein than it did in serum. The most striking difference between the electrophoretic patterns of sera and edema fluids was the marked decrease in the percentage of alpha-2 globulin in 8 of the 11 fluids compared with that present in the serum. There appeared to be no relationship between the total protein or the albumin concentrations of serum and edema fluid, whereas the percentage of albumin in the 2 fluids was directly related.

KURLAND

Linhart, J., and Prerovsky, I.: Effect of Hydergin, TAAB and Blockage of Stellate Ganglion on the Reactivity of Peripheral Veins in Myocardial Insufficiency. Cardiologia **36:** 169, 1960.

In 63 patients with chronic right ventricular failure and 33 control subjects the response of venous pressure to compression was investigated. After compression of the upper arm with a pressure of 60 mm. Hg the average rise of venous pressure on the dorsal surface of the hand within 2½ minutes was 68.7 mm. Hg in the cardiac patients as compared with 57.7 mm. Hg in the control subjects; this phenomenon was termed "overshoot" of the venous pressure. Irrespective of changes in arterial pressure, the "overshoot" was partially or wholly abolished by injections of Hydergin, tetraethylammonium bromide, or block of the stellate ganglion. Evidence is adduced that the increase in reactive changes of venous pressure are due to increased tone of walls of the veins, mediated by the nervous system. Consideration of increase in venous tone is indispensable for an explanation of the mechanism underlying the increase in venous pressure in cases of cardiac failure.

BRACHFELD

SURGERY AND CARDIOVASCULAR DISEASE

Dubourg, G., Fontan, F., Cottin, D., Mathe, P., Bricaud, H., and Broustet, P.: Cardiac Standstill through Anoxia in Extracorporeal Circulation. Arch. mal. coeur **12:** 1355, (Dec.), 1959.

The method of achieving cardiac standstill during direct heart surgery, by clamping the aorta rather than by injecting potassium, has the advantages of a completely dry operative field, no loss or hemolysis of coronary venous blood, and the possibility of temporarily reactivating the heart by releasing the clamp to check the adequacy of the sutures or the function of the conducting system. Return of activity on removing the clamp is much faster than when chemical methods are used. The disadvantage of this method is that complete relaxation is not achieved until after 5 or 6 minutes, but this is of little importance, since the first minutes are used for exploration rather than for operation. When the heart does no external work, anoxia can be tolerated for long intervals without lasting after-effects. No such effects in electrocardiographic or mechanical function appeared after standstill of up to 35 minutes in 10 dogs and 5 patients undergoing surgery with anoxia cardiac standstill. Ventricular fibrillation did not appear in any of the patients; it did appear in 6 of the dogs, but could be easily interrupted by electric defibrillation or ceased spontaneously after release of the clamp.

Anoxic cardiac arrest is accordingly considered as the method of the future.

LEPESCHKIN

Kirklin, J. W.: Surgical Treatment of Ventricular Septal Defects. Am. J. Cardiol. 5: 234 (Feb.), 1960.

Some aspects of the open-heart repair of ventricular septal defects at the Mayo Clinic since 1956 are presented. Candidates for the operation generally were those patients in whom an arteriovenous shunt was demonstrated, regardless of the height of the pulmonary artery pressure. Those younger than 2 years and not in heart failure and those who had a hemodynamically insignificant small lesion without endocarditis were not subjected to surgery. The operation was performed with the aid of a pump-oxygenator, with asystole induced by cross-clamping the aorta, and by suture closure of the defect. Postoperative care was provided in a special area. Over-all results were good, especially when considering the fact that 60 per cent of the patients had severe pulmonary hypertension. There was a residual shunt in about 5 per cent of the cases, persistent complete heart block in 5 per cent, and an in-hospital mortality rate of 5 per cent. The outlook for successful defect repair in the patient with slight or moderate pulmonary hypertension was believed to be excellent.

ROGERS

Liddle, H. V., Meyer, B. W., and Jones, J. C.: The Results of Surgical Correction of Atrial Septal Defect Complicated by Pulmonary Hypertension. J. Thoracic Surg. 39: 35 (Jan.), 1960.

Surgical correction of atrial septal defect of the secundum type has become a relatively safe procedure. The authors have repaired the defect in 140 patients with normal pulmonary artery pressure without mortality. They consider a pulmonary artery pressure in excess of 50 mm. Hg to constitute pulmonary hypertension. This particular report deals with 15 patients with simple secundum atrial defects complicated by pulmonary hypertension. Symptoms were rapidly progressive in all of the patients. Although all showed enlarged hilar vessels, there was a disproportionate diminution in the caliber of the peripheral vessels. This discrepancy was most marked in those patients who died at operation. All but 2 of these patients showed electrocardiographic evidence of marked right ventricular hypertrophy. In 1 patient with a pulmonary artery pressure of 100, there was no evidence of right ventricular hypertrophy either on the electrocardiogram or the roentgenogram. Even in the most severe instances of pulmonary vascular obstruction, pulmonary artery pressure never exceeded systemic arterial pressure. In most of these patients the size of the left-to-right shunt was reduced. Two patients were treated by Sandergaard circumclusion, 3 by atrioseptopexy, and 10 were closed under direct vision employing hypothermia. In 4 patients immediately on closure of the defect the right ventricle dilated acutely, fibrillated, and could not be restored. A fifth patient tolerated the closure but at the conclusion the left ventricle ruptured. Two patients who survived were not helped by the procedure. Of the 8 patients who tolerated the closure, 1 died postoperatively of hemorrhage from the internal mammary artery. A second has had reopening of the atrial septal defect with progressive pulmonary hypertension. The 6 remaining patients have all benefited. There was no correlation between the size of the defect and the appearance of pulmonary hypertension. The high risk in these patients makes careful selection of those for surgical intervention very important. The unfavorable signs are cyanosis, history of cardiac failure, great disproportion between hilar and peripheral pulmonary vessels, and electrocardiographic evidence of severe right ventricular hypertrophy. The presence of the first factors indicate that the patient will probably not survive the operation. It is recommended that because of the poor risk in these patients compared to the uncomplicated situation, the defects should be closed when they are recognized.

LEVINSON

Sirak, H. D., Meckstroth, C. V. Ryan, J. M., Claassen, L. G., and Hosier, D. M.: The Prevention of Heart Block in the Surgical Repair of Interventricular Septal Defect. J. Thoracic Surg. 39:229 (Feb.), 1960.

If the complication of heart block could be eliminated, the surgical risk in these cases would be minimal and it would be justifiable to recommend the operation for less seriously ill patients. In the experience of the authors, heart block has not occurred in their series of 53 patients with interventricular septal defect. They believe that their technic seems to have eliminated this problem while providing a reliable method for obtaining complete closure of each type of defect. In addition to the pulmonary hypertensive group, they have operated on those patients who have evidence of large left-to-right shunts. It is their opinion that the employment of a plastic patch is important, particularly in the larger defects or when the septal rim is thin because it tends to reduce the tension on the sutures. Such tension may cause edema and punctate hemorrhage, increasing the likelihood of conduction disturbances.

Also the possible role of injury from patch compression has not been sufficiently stressed. The most satisfactory cloth patch has proved to be one consisting of 2 components: Polyvinyl (Ivalon sponge) and Teflon felt. It provides the desired cushion effect and applies itself evenly to the contours of the septal rim. The Teflon felt faces the cavity of the right ventricle. It holds sutures well, is flexible, and provides the needed strength for the patch. Thus a firm repair of the larger defects is obtained without having to tighten the sutures excessively and risk crushing the septum. For defects around 1 cm. in size, a cigarette-shaped piece of noncompressed Polyvinyl sponge has been used. Mersiline sutures have been employed as an additional precautionary measure because of their smoother surface and lower tissue reactivity. In those under 1 year of age cardiac bypass was avoided, and a band was placed about the main pulmonary artery to reduce the left-to-right shunt. After the child was older the construction in the pulmonary artery and the septal defect were corrected. In 2 of the patients a sizable left-to-right shunt presisted. In 1 patient only 8 traumatic silk sutures were used, and it was thought that these sutures disrupted postoperatively. A second failure may have been due to the inability of the Teflon cloth to apply itself snugly to the septum. In 3 patients there was a residual grade I to II systolic murmur over the pulmonic area, which may have resulted from an overlooked defect. There were 9 deaths in the series. The mortality in this group was largely in those showing high resistance in the pulmonary vascular bed. In 1 patient there was an overlooked large patent ductus and atrial septal defect; the other was a 3-month-old infant who would now be submitted to the 2-stage procedure as noted above. There were no deaths attributable to heart block, which is thought to be due to the type of repair employed in this procedure.

LEVINSON

UNCOMMON FORMS OF HEART DISEASE

Gorlin, R., Brachfeld, N., Turner, J. D., Messer, J. V., and Salazer, E.: The Idiopathic High Cardiac Output State. J. Clin. Invest. 38:2144 (Dec.), 1959.

Hemodynamic observations were made in a group of 8 males, aged 17 to 48 years, who had the following clinical features in common: a precordial systolic murmur; hyperkinetic heart and arteries; ventricular hypertrophy by electrocardiogram; and, frequently, pulmonary plethora by x-ray. Cardiac catheterization revealed a persistently elevated cardiac output and peripheral vasodilatation. The elevated cardiac output was confirmed on 30 separate determinations including rest, sedation, and sleep in selected cases. Blood chemical studies carried out included arterial oxygen saturation, pCO_2 and pH which were all normal. Blood lactate and pyruvate and catechol amine levels were normal at rest and on effort. Thyroid studies were normal in all 8 patients. Circulating blood volume was within normal limits in 6 of 7 patients. Multiple diagnostic technics failed to reveal any left-to-right shunt within the heart or great vessels in each of the 8 patients. By these studies the usual causes of the high output state, arteriovenous fistula, arterial anoxemia and anemia, metabolic or hormonal alterations in vasomotor tone and blood flow distributions were eliminated. It is suggested that the association of a high-output state with cardiac murmur, cardiac hyperactivity, and hypertrophy represent a distinct clinicophysiologic syndrome.

KAYDEN

Herbst, M., Hartleb, O., and Bock, K.: Clinical and Angiocardiographic Confirmation of the Bernheim Syndrome. Fortschr. Röntgenstr., 48:997, 1959.

In 5 patients with marked left ventricular hypertrophy due to valvular, supravalvular, or isthmic aortic stenosis, angiocardiography disclosed definite narrowing of the right ventricle by the bulging left ventricle as well as a pressure gradient between right ventricle and pulmonary artery ranging from 2 to 53 mm. In the patient with the highest gradient, who was at first diagnosed as having infundibular pulmonary stenosis, signs of right ventricular failure without those of left ventricular failure were present. The other 4 patients showed an asymptomatic phase of the Bernheim syndrome. The electrocardiograms in 3 of the patients with the highest gradients showed right axis deviation or axis inversion, with a negative QRS complex in the first 4 to 7 precordial leads.

LEPESCHKIN

Howard, E. J.: Chronic Atrial Fibrillation Unrelated to Organic Heart Disease: Follow-up Study of Five Cases. Am. Heart J. 59:343 (Mar.), 1960.

Five patients with chronic atrial fibrillation from 11 months to 14 years are reported. In none was there substantial evidence of underlying heart disease as the factor responsible for the abnormal rhythm. Each of these patients, however, did have a personality disorder confirmed by psychiatric evaluation. Four of the patients required permanent digitalis therapy. In 2 pa-

tients congestive heart failure and left ventricular enlargement complicated the atrial fibrillation. SAGALL

Voridis, E., and Maurice, P.: Familial cardiomegaly. Arch. mal. coeur 12:1410, (Dec.) 1959.

Two brothers and a sister 52 to 56 years of age are described who showed marked left ventricular and atrial hypertrophy and electrocardiographic signs of left ventricular and atrial hypertrophy with incomplete left bundle-branch block, without any apparent cause. Study of the 10 families with familial cardiomegaly reported up to the present showed that 64.2 per cent of the children developed this condition; the hereditary factor accordingly appears to be a dominant one. LEPESCHKIN

VALVULAR HEART DISEASE

Carleton, R. A., Levinson G. E., Abelmann, W. H.: Assessment of Mitral Regurgitation by Indicator Dilution: Observations on the Principle of Korner and Shillingford. Am. Heart J. 58:663 (Nov.), 1959.

In 1955 and 1956, Korner and Shillingford, working with indicator-dilution curves in a circulatory model, proposed a statistical approach to the quantification of valvular regurgitation. In the present communication, a clinical study of the variance method of Korner and Shillingford is reported. It was found that their basic principle was valid, namely, that mitral regurgitation determinably alters the parameters of indicator-dilution curves independently of the effects of flow and central volume. However, it was apparent that in many patients regurgitant flow as determined by this variance method was grossly overestimated. The results could be used as a means of grading the severity of mitral regurgitation in a given patient with reference to a group of patients, but the calculated numerical values did not represent actual regurgitant flows. An analysis of the requirements of the variance method suggested that the validity of the basic principle could be preserved and more physiologic results obtained by the use of a volume which was more closely related to the mixing phenomenon. SAGALL

Colvez, P., Alhomme, P., Samson, M., and Guedon, J.: Left Ventricular Filling Pressure in Advanced Aortic Insufficiency; Its Relation to Prolongation of Atrio-ventricular Conduction. Arch. mal coeur 12:1369, (Dec.), 1959.

Two patients who developed marked aortic regurgitation suddenly (from bacterial endocarditis and during valvulotomy for aortic stenosis) also developed prolongation of the P-R interval at the same time. Of 219 patients with aortic regurgitation, 37 per cent had a prolonged P-R interval. It is possible that this prolongation resulted from the increased diastolic left ventricular pressure. In aortic and mitral regurgitation, where this pressure is less increased than in pure aortic regurgitation, the incidence of P-R prolongation was only 20 per cent. The increased diastolic pressure leads to premature closure of the mitral valve, and the prolongation of the P-R interval can have a beneficial effect in such cases, since it enables atrial contraction to occur before the mitral valves are closed.

LEPESCHKIN

Gilbert, J. W., Morrow, A. G., and Braunwald, E.: Results of Open Commissurotomy in Acquired Calcific Stenosis: Clinical and Hemodynamic Studies in Patients Operated upon with Genenral Hypothermia. Ann. Surg. 151:1 (Jan.), 1960.

Aortic valvular surgery remains a very formidable procedure. Thirteen patients, aged 30 to 52, with calcific aortic stenosis are reported. The clinical and physiologic findings were noted before and after open operation with general hypothermia. Dyspnea was the most outstanding symptom. Other symptoms were angina, fatigability, and syncope. In the 3 patients who had had transient episodes of atrial fibrillation, mitral as well as aortic valve disease was present. Electrocardiographic evidence of left ventricular hypertrophy was found in all but 1 patient. The typical systolic ejection murmur was heard in all patients. The peak systolic gradients across the aortic valve ranged from 40 to 133 mm. Hg. In 8 patients with isolated aortic valve disease the cardiac output at rest was normal in 6. The aortic valve surgery was carried out with interruption of the circulation ranging from 2 to 4.5 minutes with an esophageal temperature of 29 to 30 C. Post-stenotic dilatation of the aorta was noted in all patients, the degree corresponding with the magnitude of the systolic gradient across the aortic valve. Function seemed best preserved by opening the commissures in such a manner as to fashion a bicuspid valve. There were 4 deaths in the 13 patients. Refractory ventricular fibrillation occurred in 2 of these, irreversible hypotension in 1 and pulmonary embolization in another. Two of these 4 patients had combined mitral and aortic commissurotomy. Of the 9 survivors, who have been followed from 2 to 29 months, all are alive and have been subjectively improved. Six of these have been markedly improved. No patient has experienced syncope after operation, and of the 7 with preoperative angina

this symptom has been completely abolished in 4 and markedly reduced in 3. The peak systolic gradient across the aortic valve was significantly reduced in 8 of the 9 survivors. In the 4 patients who died, marked calcification with great distortion of the anatomic landmarks of the aortic valve was noted at postmortem examination. With the short interval for surgery here, a compromise between obstruction and regurgitation must often be sought. A history of left ventricular failure carries an ominous prognosis. Blood loss, hypotension, and the production of aortic regurgitation are poorly tolerated. It is suggested that a more prolonged procedure, employing extracorporeal circulation, would be merited only when a satisfactory prosthesis is available for valve replacement.

LEVINSON

Glenn, F., and Redo, S. F.: Mitral Stenosis and Biliary Tract Disease. Ann. Surg. 151:139 (Jan.), 1960.

This paper deals with a previous report of 300 patients operated on for mitral disease and the present report of 100 patients. In the original series 43 (14.3 per cent) patients had gallbladder disease established beyond doubt. In the present series 18 per cent had definite gallbladder disease. The latter group were more thoroughly evaluated for gallbladder disease. The point is made that when gallblader disease exists, it is preferable to do the gallbladder surgery first if possible. It has been noted that acute cholecystitis may be precipitated in a diseased gallbladder by mitral commissurotomy. It is thought that this is produced by a period of fasting which results in very viscid bile which can be more irritating to the mucous membrane. This is believed to initiate an inflammatory reaction with occlusion of the cystic duct and acute cholecystitis. A case report is cited in which the cholecystogram, prior to mitral valvulotomy, was normal. Following the heart surgery there was acute right upper quadrant pain with leukocytosis. At this time the gallbladder could not be visualized on cholecystography, and cholecystography was done a month later. Pathologic examination revealed a chronically inflamed gallbladder. It is suggested that cholecystography be done routinely as a preoperative measure in patients undergoing mitral valve surgery so that occurrence of postoperative pain may better be evaluated by cholecystography. The incidence of gallbladder disease as shown in these patients is significantly higher than in a segment of the general population of similar age group. It is postulated that the underlying etiologic factor may be transient episodes of right heart failure resulting in enough disturbance in liver function to produce changes in the gallbladder favorable to the precipitation of cholesterol in crystalline form.

LEVINSON

Kelly, E. R., Morrow, A. G., and Braunwald, E.: Catheterization of the Left Side of the Heart: A Key to the Solution of Some Perplexing Problems in Cardiovascular Diagnosis and Management. New England J. Med. 262:162 (Jan. 28), 1960.

Seven cases are reported to demonstrate the usefulness of catheterization of the left side of the heart in the clinical management of patients with unusual manifestations of relatively common forms of acquired heart disease. The procedure proved to be of value in the detection of occult mitral stenosis producing severe congestive heart failure, which was relieved by commissurotomy; in the finding of hemodynamically mild mitral stenosis and aortic stenosis when physical findings suggested severe valvular obstruction and the need for surgery; in the separation of "mixed" mitral lesions with identification of predominant mitral regurgitation; in revealing myocardial disease which simulated valvular heart disease; and in the solution to an unusual hemodynamic and clinical problem of aortic-valve disease.

SAGALL

Levinson, G. E., Carleton, R. A., and Abelmann, W. H.: Assessment of Mitral Regurgitation by Indicator Dilution: An Analysis of the Determinants of the Abnormal Dilution Curve. Am. Heart J. 58:873 (Dec.), 1959.

An analysis was made of the indicator-dilution curves obtained by left atrium injections in 5 normal patients and 33 patients with compensated rheumatic mitral valvular disease. The data revealed that the parameters of the dilution curve, which are sensitive both to the increase in volume of the left side of the heart and to the specific effect of regurgitation, were of help in distinguishing patients with and without predominant mitral regurgitation. The parameters that reflected only the increase in volume had only limited discriminative values. It was further shown that mitral regurgitation in man differs strikingly from that of the experimental model in that the volume of the left side of the heart is a dependent variable of the severity of the regurgitation and an increase in this volume is the chief determinant of the abnormal dilution curves found in this condition. The simple indices of help in distinguishing between predominant mitral stenosis and predominant mitral regurgitation after dye is injected into the left atrium were the disappearance time, the reciprocal of the slope, the "residual" volume, the ratio of concen-

tration, and the ratio of "residual" volume to stroke volume.

SAGALL

VASCULAR DISEASE

Crawford, E. S., De Bakey, M. E., Morris, G. C., Jr., and Garrett, E.: Evaluation of Late Failures after Reconstructive Operations for Occlusive Lesions of the Aorta and Iliac, Femoral, and Popliteal Arteries. Surgery 47:79 (Jan.), 1960.

Late failure after arterial reconstruction in the aorto-iliac area occurred in 38 (6.2 per cent) of 611 patients. One hundred and nine (21 per cent) of 515 with femoropopliteal operations were also unsuccessful. These failures occurred from 1 week to 5½ years after discharge from hospital. Late failures in the patients with aorto-iliac operations for the most part occurred within 2 years after operation. Homografts were associated with a higher incidence of failure resulting from aortoduodenal fistula, narrowed anastomosis, and recurrent obstruction. Aneurysmal deterioration occurred in 2 homografts. When Nylon tubes were used, failure was often due to the development of false aneurysms and obstruction from kinking of the graft. The use of Dacron as a bypass graft with additional surgical experience, has resulted in a higher incidence of long-term function. Most of the failures in operations for femoropopliteal occlusion occurred within the first year. Fifty-two per cent of patients with homografts, 32 per cent with Nylon, and 11 per cent with Dacron prostheses sustained late failure. Endarterectomy alone was carried out in a few patients with short, discrete, well-localized lesions; failure occurred in 15 per cent of these. All failures with Dacron tubes occurred during the first 18 months. Eighty-nine patients in this group were reexamined. In almost half of these, failure was due to underlying arterial disease. Recurrent obstruction occurred proximal to the region of operation in one third, and distal to the previous operative site in the remainder. In the other half of the patients who were followed up, failure was due to technical surgical factors similar to those seen in the aorto-iliac operations. A normal pulsatile blood flow was restored in 58 of the 64 patients who were re-operated upon. Eight of these patients have had recurrent failure up to 12 months postoperatively. The remainder have been followed up to 56 months. A third operation was performed successfully in 5 of these 8 patients. In some recent patients seen very soon after graft occlusion (up to 5 days) the popliteal artery was explored even though on arteriogram it was seen to be completely occluded. Transection of the occluded graft proximal to the distal anastomosis was carried out, and the thrombi were removed from the tube and the distal popliteal artery. A similar procedure was carried out on the proximal anastomosis and then a new graft was sutured to the ends of the short segments of the previous graft. In those patients with recurrent obstruction the symptoms at the time of recurrence were often not so severe as those prior to the original operation, indicating a significant degree of improvement after a temporary period of graft function.

SHEPS

Hasse, H. M., Rau, G., and Schoop, W.: Significance of Pressure and Flow for the Dilatation of Collateral Blood Vessels in Arterial Occlusion. Ztschr. Kreislaufforsch. 48:1127 (Dec.), 1959.

If dilatation of collateral arteries were dependent on the increase of systolic pressure resulting from reflection of the pulse wave at the point of occlusion, the artery proximal to the occlusion as well as all of its branches originating in this region would be dilated. However, the usual behavior, illustrated in a patient with occlusion of the superficial femoral artery, is that the occluded artery proximal from the occlusion is very narrow while only the distal branches originating in this region are dilated and show a serpentine course. This observation favors the interpretation that it is the increased blood velocity that causes dilatation rather than increased blood pressure. This interpretation is in keeping with the observation that the greatest dilatation takes place in arteriovenous aneurysms, where pressure is especially low and blood velocity especially high.

LEPESCHKIN

Keisker, H. W., and Bowers, R. F.: Results Obtained by Superficial Femoral Vein Ligation. Surgery 47:224 (Feb.), 1960.

Superficial ligation of the femoral vein was carried out on 158 patients with a mortality rate of 1.3 per cent. One patient died 7 hours postoperatively from a pulmonary embolus that had occurred preoperatively; another died 10 days postoperatively, and at autopsy there were thromboses of the prostatic vein and a myocardial infarction. Eighty-six patients were followed for 2 to 10 years. Seven patients later sustained pulmonary emboli at long intervals. There was mild swelling of the leg in 38 patients and severe swelling in 10 patients. Severe swelling was associated with induration and ulceration. Ten patients sustained leg ulcers postoperatively. Three of these had had prior ulcerations. The authors suggest that superficial femoral vein ligation is associated with a low mortality and morbidity

and is used by them when phlebothrombosis is present or strongly suspected and if anticoagulant therapy cannot be given, proper anticoagulation fails, and phlebothrombosis or thrombophlebitis returns following cessation of anticoagulant therapy.

SHEPS

Klass, A. A.: Intestinal Angina and Infarction. Canad. M. A. J. 82:620 (Mar. 19), 1960.

Prior to 1950 mesenteric arterial occlusive disease was seldom diagnosed ante mortem, but now the clinical findings are better recognized. Acute occlusion with infarction produces rapid onset of abdominal pain in an older person who appears gravely ill, has diffuse abdominal tenderness and firmness without distention, and whose plain abdominal roentgenograms are unremarkable. If recognized within 48 hours of onset, laparotomy is often indicated and reveals little change in the bowel. The superior mesenteric artery then should be explored. The obstruction, if present, will usually be removable, since it ordinarily involves only the initial portion of the vessel. Lesions of other abdominal arteries are of much less importance in causing intestinal ischemia. For 2 to 3 days after successful restoration of circulation, the patient needs close observation for evidence of intestinal gangrene or perforation; if doubt arises repeat laparotomy may be necessary. Partial mesenteric arterial occlusion occasionally causes dull, intermittent, mid-abdominal pain, sometimes radiating to the back after a large meal. Associated diarrhea containing fat and undigested muscle, weight loss, and no definite roentgen abnormality may lead to a mistaken impression of "malabsorption syndrome" or "irritable colon." Superior mesenteric thrombendarterectomy has produced relief for a year or longer, but should not be proposed until thorough medical evaluation and a trial of medical treatment have been carried out.

ROGERS

Richardson, J. C.: Pitfalls in Diagnosis and Treatment of Cerebral Arterial Insufficiency. Canad. M. A. J. 82:298 (Feb. 6), 1960.

Current views of the clinical aspects of degenerative cerebrovascular disease were summarized, and some diagnostic difficulties were illustrated in 5 case reports. Localization of the vascular lesion in major or minor strokes has become important because a significant minority, involving particularly the carotid or vertebral arteries, may be benefited surgically. While percutaneous arteriography has been of great value in documenting these lesions, it has continued to be somewhat hazardous, and judgment is required in the selection of cases for its use. Careful history and physical examination continue to be of first importance in evaluating these patients, supplemented by analysis of the cerebrospinal fluid for evidence of bleeding, and by electroencephalography, and ophthalmodynamometry. The clinical diagnosis of a stroke as being non-hemorrhagic was found at autopsy to be erroneous in nearly one half the instances. Therefore, caution was advised in the use of anticoagulant therapy especially in the presence of hypertension which increased the likelihood of hemorrhage in the damaged brain.

ROGERS

Ten Eyck, F. W., Osmundson, P. J., Brandenburg, R. O., and Edwards, J. E.: Aneurysms of the Abdominal Aorta and Fever. Proc. Staff Meet., Mayo Clin. 35:1 (Jan. 6), 1960.

When patients with abdominal aneurysms develop fever, the presence of bacterial infection should be suspected. Positive blood cultures would lend support to this impression. Rupture of an aneurysm is very likely once it becomes infected, even with abundant antibiotic therapy. Therefore, in any patient with an abdominal aneurysm prophylactic antibiotic therapy should be used if bacteremia is likely to develop. In addition, prompt and intensive antibiotic treatment is recommended when a potentially significant bacterial infection is apparent anywhere in the body of a patient with a nonresectable abdominal aneurysm.

KRAUSE

Whitman, E. J., James, J. M., Ivins, J. C., and Johnson, E. W., Jr.: Femoral Bypass Grafts. Surgery 47:29 (Jan.), 1960.

The experience of the Mayo Clinic in the use of femoral bypass grafts utilizing homografts, Nylon and Teflon materials is reviewed in detail. Homografts have been discarded because (1) they degenerate in time; (2) an adequate supply is not always available; (3) they present problems in storage, preservation, and sterilization; and (4) one cannot always choose a proper size in each case. The Nylon grafts were discarded because acute thrombosis occurred either immediately after the operation or within the next year in a large proportion of the cases. Teflon was the material of choice because of reduced tissue reaction and reduced incidence of thrombosis during the follow-up period. At this time woven Teflon seems to be the material of choice in terms of technical ease and long-term function.

SHEPS

NEWS FROM THE AMERICAN HEART ASSOCIATION

44 East 23rd Street, New York 10, New York
Telephone Gramercy 7-9170

May 15 is Abstracts Deadline For 1961 AHA Scientific Sessions

May 15, 1961, is the deadline for submitting abstracts of papers to be presented at the Annual Scientific Sessions of the American Heart Association in Bal Harbour, Florida, October 20-22, 1961. Official application forms may be obtained from Richard E. Hurley, M.D., Medical Associate, American Heart Association, 44 East 23rd Street, New York 10, New York.

Papers intended for presentation must be based on original investigations in, or related to, the cardiovascular field. Abstracts must be limited to 250 words or less and include a brief digest of the results obtained and conclusions reached.

Applications for space for *scientific exhibits*, which must be returned postmarked not later than May 15, 1961, may also be obtained from Dr. Hurley. Space for *industrial exhibits* may be requested through Steven K. Herlitz, Inc. 280 Madison Avenue, New York 16, New York.

Abstracts of Papers Due May 15 for Arteriosclerosis Council Meeting

The AHA Council on Arteriosclerosis will hold its Annual Meeting October 18-20, 1961, immediately preceding the American Heart Association's Annual Scientific Sessions at Bal Harbour, Florida.

May 15, 1961, is the deadline for submitting abstracts of papers for presentation at the Council sessions. Abstracts must be limited to 250 words. Official application forms may be obtained from Jeremiah Stamler, M.D., Chicago Board of Health, 54 West Hubbard Street, Chicago 10, Illinois. Forms may also be obtained from the American Heart Association, 44 East 23rd Street, New York 10, New York.

The Council sessions will be open to all interested individuals whether or not they are Council members. Abstracts of papers for presentation are invited from members and non-members alike.

National Research Supplemented By Local Heart Associations

The Association's affiliates and chapters have contributed a new high of $104,644 for supplementary support of national research awards in fiscal 1960-61. These funds make possible the financing of approved studies which could not otherwise be covered by the national research budget.

In addition to those previously reported, sums have been received from the following:

Norwalk (Conn.) Heart Association, $8000 in partial support of the grants to Dr. Michael Hume, Yale University School of Medicine, and Dr. Francis Dammann, University of Virginia; Waterbury (Conn.) Area Heart Association, $3000 in partial support of the grant of Dr. Levin L. Watters, Yale University School of Medicine; and Idaho Heart Association, $3840 in partial support of the work of Dr. Robert F. Rushmer, University of Washington School of Medicine, Dr.

Arthur J. Seaman, University of Oregon Medical School, and Drs. John J. Osborn and Mogens L. Bramson, San Francisco Institute of Medical Sciences.

10 U. S. Physicians Chosen as Directors For Inter-American Cardiology Society

Ten representatives from the United States have been elected to serve four-year terms on the Council of Directors of the Inter-American Society of Cardiology. At the Society's meeting in Rio de Janeiro last August, E. Cowles Andrus, M.D., of Baltimore, was chosen Vice President and Irvine H. Page, M.D., of Cleveland, Assistant Secretary-Treasurer.

Other U. S. representatives who will serve on the Council are: Paul Camp, M.D., Richmond, Virginia; Clarence de la Chapelle, M.D., New York; George C. Griffith, M.D., Los Angeles; Edgar Hull, M.D., New Orleans; Benjamin I. Johnstone, M.D., Detroit; Homer Rush, M.D., Portland, Oregon; John Sampson, M.D., San Francisco; and Robert W. Wilkins, M.D., Boston.

The Society's Council of Directors consists of 24 members, 12 representing the English speaking countries and the remainder Spanish and Portuguese speaking countries.

Need for More Research Funds Stressed in AHA 1960 Annual Report

Contradicting published statements that the availability of funds for medical research has outstripped the availability of qualified investigators to use them properly, the recently-issued 1960 Annual Report of the American Heart Association states that "double the sums now available could be used effectively to speed the conquest of heart diseases."

Despite the Association's record-breaking research expenditure of more than $9,000,000 in fiscal 1959-60, funds were lacking to support all grants approved as scientifically worthwhile by the national Research Committee and the number of new Career Investigator appointments had to be limited to two, the Report notes.

Entitled "Your Heart Fund Dollar," the Report is dedicated to all Heart volunteers whose selfless efforts over the past 12 years have established national and international leadership by the American Heart Association in the attack on cardiovascular diseases.

Heart Bulletin Available to Physicians Through Local Heart Associations

The Heart Bulletin for January-February 1961 has been published and is now available to physicians through most local affiliated Heart Associations.

Contents for this issue include articles on "Promises of Recent Cardiovascular Research," by George E. Wakerlin, M.D., Ph.D., Medical Director of the American Heart Association; "The Effects of Smoking on Normal Persons and Patients with Hypertension," by Grace M. Roth, Ph.D., and Richard M. Shick, M.D., and "Some Determinants of Renal Function in Patients with 'Unilateral Renal Disease'," by Harriet Dustan, M.D.

The Bulletin is sponsored by the Association in cooperation with the National Heart Institute and American Academy of General Practice.

Hospital House Staffs to Receive "Modern Concepts of CV Disease"

Heart Associations throughout the country have been urged to make available to house staff members of all hospitals in their areas copies of the Association's monthly publication, *Modern Concepts of Cardiovascular Disease*, each issue of which is devoted to some single aspect of cardiovascular medicine.

Dr. E. Cowles Andrus, Professor of Medicine, Johns Hopkins University School of Medicine and a former President of the American Heart Association, became the publication's editor on January 1, 1961, succeeding Dr. Howard P. Lewis who has been editor since 1956.

Form Pediatric Cardiology Sub-Board

Organization has been completed of the Sub-Board of Pediatric Cardiology of the American Board of Pediatrics and applica-

tions are now being accepted for certification both on report and by examination. Applications are also being received for approval of residency training programs.

Sub-Board members are: James W. DuShane, M.D., Chairman, Rochester, Minnesota; Forrest H. Adams, M.D., Los Angeles; Edward C. Lambert, M.D., Buffalo; Alexander S. Nadas, M.D., Boston; Saul J. Robinson, M.D., San Francisco; and Helen B. Taussig, M.D., Baltimore.

Further information and application forms are obtainable from John McK. Mitchell, M.D., Executive Secretary, American Board of Pediatrics, 6 Cushman Road, Rosemont, Pennsylvania.

Cardiovascular Agents Handbook Issued

An *Index-Handbook of Cardiovascular Agents* (Volume II, 1951-55) for use by physicians and scientists in the field of cardiovascular physiology and pharmacology, cardiology and related aspects of internal medicine, has been published by the Cardiovascular Literature Project of the National Academy of Science-National Research Council.

The handbook comprises more than 100,000 index entries in alphabetical order and special features involving standardization of chemical names, translation of titles of papers with identification as to original languages, and extensive cross-references of standardized biological and medical subject headings.

Copies are available at $15 from the Publications Office, NAS-NRC, 2101 Constitution Avenue, N. W., Washington 25, D.C. Volumes I (1931-50) and III (1956-60) are now in preparation. Isaac D. Welt, Ph.D., Project Director, will welcome correspondence regarding the handbook.

European Cardiology Congress Proceedings

Proceedings of the Third European Congress of Cardiology, held in Rome, September, 1960, are now available from Excerpta Medica Foundation, 2 East 103rd Street, New York 29, New York. In three volumes containing 1824 pages and 395 illustrations, the Proceedings are priced at $40.

Meetings Calendar

April 10-14: American Physiological Society, Atlantic City. Ray G. Daggs, 9650 Wisconsin Ave., Washington 14, D.C.

April 17-20: American Academy of General Practice, Miami Beach. Mac F. Cahal, Volker at Brookside, Kansas City 12, Missouri.

April 24-26: American Association for Thoracic Surgery, Philadelphia. Miss Ada Harvey, 7730 Carondelet Ave., St. Louis 5, Missouri.

April 28-30: American Psychosomatic Society, Atlantic City. Morton F. Reiser, 265 Nassau Rd., Roosevelt, New York.

April 30: American Federation for Clinical Research, Atlantic City. James E. Bryan, 250 W. 57th St., New York 19, New York.

May 2-3: Association of American Physicians, Atlantic City. Paul Beeson, Yale University School of Medicine, New Haven 11, Connecticut.

May 5-7: American Society of Internal Medicine, Miami Beach. G. T. Bates, 350 Post St., San Francisco 8, California.

May 7-11: International College of Surgeons, North American Federation, Annual Congress, Chicago. H. E. Turner, 1516 Lake Shore Dr., Chicago 11, Illinois.

May 8-12 American College of Physicians, Miami Beach. E. C. Rosenow, Jr., 4200 Pine St., Philadelphia 4, Pennsylvania.

May 16-20: American College of Cardiology, New York. Philip Reichert, 350 Fifth Ave., New York 1, New York.

May 31-June 2: Canadian Federation of Biological Societies, Guelph, Ontario. E. H. Bensley, 1650 Cedar Ave., Montreal 25, Canada.

June 22-26: American College of Chest Physicians, New York. Murray Kornfeld, 112 E. Chestnut St., Chicago 11, Illinois.

June 23-25: American College of Angiology, New York. Alfred Halpern, 11 Hampton Court, Great Neck, New York.

June 25: Society for Vascular Surgery, New York. George H. Yeager, 314 Medical Arts Bldg., Baltimore 1, Maryland.

June 26-30: American Medical Association, Annual Meeting, New York. F. J. L. Blasingame, 535 N. Dearborn, Chicago 10, Illinois.

July 1-4: International College of Surgeons, New England Regional Meeting, Chatham, Massachusetts. M. L. Brodny, 4646 N. Marine Dr., Chicago 40, Illinois.

August 7-10: National Medical Association, New York. John T. Givens, 1108 Church St., Norfolk, Virginia.

August 27-September 1: American Congress of Physical Medicine and Rehabilitation, Cleveland. Dorothea C. Augustin, 30 N. Michigan, Chicago 2, Illinois.

September 26-29: American Roentgen Ray Society, Miami Beach. C. A. Good, Mayo Clinic, Rochester, Minnesota.

October 2-6: American College of Surgeons, Chicago. Wm. E. Adams, 40 East Erie St., Chicago 11, Illinois.

October 20-24: American Heart Association, Annual Meeting and Scientific Sessions (October 20-22), Bal Harbour, Florida. American Heart Association, 44 East 23rd St., New York 10, New York.

November 13-17: American Public Health Association, Detroit. Berwin F. Mattison, 1790 Broadway, New York 19, New York.

November 16-18: International Symposium "Etiology of Myocardial Infarction," Detroit. Thomas N. James, Henry Ford Hospital, Detroit 2, Michigan.

Abroad

April 7-9: German Society for Circulatory Research, Bad Nauheim. Prof. R. Thauer, William G. Kerckhoff Institute Der Max-Planck-Gesellschaft, Bad Nauheim, W. Germany.

June 2-5: Latin-American Congress of Physical Medicine, Lisbon. C. L. deVictoria, 245 E. 17th St., New York, New York.

June 3-15: International Medical-Surgical Meetings, Turin, Italy. Minerva Medica, Corao Bramante 85, Turin.

August 22-25: International Pharmacological Meeting (First) Stockholm. A. Wretlind, Karolinska Institutet, Stockholm 60, Sweden.

September 3-10: Inter-American Congress of Radiology, Sao Paulo. W. Bomfim-Pontes, Rua Cesario Motta, No. 112, Sao Paulo, Brazil.

September 4-7: International Congress on Rheumatology, Rome. Prof. C. B. Ballabio, Clinica Medica Generale, Via F. Sforza 35, Milano, Italy.

September 4-9: International Congress of Angiology, Prague. Prof. Z. Reinis, IVth Medical Clinic, Praha 2/499, Czechoslovakia.

September 6-12: International Congress of Human Genetics, Rome. Luigi Gedda, 5 Piazza Galeno, Rome, Italy.

September 10-15: International Neurological Congress, Rome. G. Alema, Viale Universita, 30 Rome, Italy.

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October 7-13: Fourth World Congress of Cardiology, Mexico City. I. Costero, Ave. Cuauhtemoc 300, Mexico, D.F.

CONTRIBUTORS TO THIS ISSUE

Robert F. Ackerman, M.D.
Assistant Professor of Preventive Medicine and Medicine, University of Tennessee College of Medicine, Memphis, Tennessee.

Richard J. Bing, M.D.
McGregor Professor of Medicine; Chairman, Department of Medicine, Wayne State University College of Medicine, Detroit, Michigan.

Eugene Braunwald, M.D.
Chief, Section of Cardiology, Clinic of Surgery, National Heart Institute, Bethesda, Maryland.

Cesar A. Caceres, M.D.
Special Research Fellow, The George Washington University Hospital, Washington, D.C. Presently: Chief, Instrumentation Unit, Heart Disease Control Program, U.S. Public Health Service, Washington, D.C.

C. A. Chidsey III, M.D.
Clinical Associate, National Heart Institute, National Institutes of Health, Bethesda, Maryland.

R. Clauss, M.D.
Associate Professor of Surgery, New York University School of Medicine; Associate Visiting Surgeon, Bellevue Hospital, New York, New York.

A. Cournand, M.D.
Professor of Medicine, Columbia University College of Physicians and Surgeons; Director, Cardio-Pulmonary Laboratory (Columbia University Division) Bellevue Hospital, New York, New York.

James W. DuShane, M.D.
Consultant, Section of Pediatrics, Mayo Clinic; Associate Professor of Pediatrics, Mayo Foundation, Graduate School, University of Minnesota, Rochester, Minnesota.

Jesse E. Edwards, M.D.
Consultant, Section of Pathologic Anatomy, Mayo Clinic; Professor of Pathology, Mayo Foundation, Graduate School, University of Minnesota, Rochester, Minnesota. Presently, Director of Laboratories, Charles T. Miller Hospital, St. Paul, Minnesota.

Frederick P. Feder, M.D.
Presently, Intern in Surgery, Strong Memorial Hospital, Rochester, New York.

Martin J. Frank, M.D.
Research Fellow, Seton Hall College of Medicine, Jersey City, New Jersey.

Charles K. Friedberg, M.D.
Attending Physician for Cardiology and Chief of Cardiology, The Mount Sinai Hospital, New York; Associate Professor of Medicine, Columbia University College of Physicians and Surgeons, New York.

H. W. Fritts, Jr., M.D.
Associate Professor of Medicine, Columbia University College of Physicians and Surgeons; Associate Visiting Physician, (Columbia University Division) Bellevue Hospital, New York, New York.

Robert L. Frye, M.D.
Section of Cardiology, Clinic of Surgery, National Heart Institute, Bethesda, Maryland. Present address: Johns Hopkins Hospital, Baltimore, Maryland.

Peter C. Gazes, M.D.
Assistant Professor of Medicine, Medical College of South Carolina, Charleston, South Carolina.

Gilbert Greenspan, M.D.
Resident Physician in Internal Medicine, Los Angeles County Harbor General Hospital, Torrance, California.

Sigmund N. Groch, M.D.
Assistant Professor of Clinical Medicine, Cornell University College of Medicine; Associate Visiting Physician—Bellevue Hospital; Physician to Out-Patients, The New York Hospital; Director, Cerebral Vascular Disease Study, Bellevue Hospital, New York City, New York.

P. Harris, M.D.
Senior Lecturer in Medicine, University of Birmingham; Honorary Consultant Physician, United Birmingham Hospitals, Birmingham, England. Fellow of the Nuffield Foundation.

Harper K. Hellems, M.D.
Professor of Medicine, Seton Hall College of Medicine, Jersey City, New Jersey.

Walter S. Henly, M.D.
Assistant Professor of Surgery, Baylor University College of Medicine, Houston, Texas. Established Investigator of the American Heart Association.

Charles R. Holmes, M.D.
Former Resident, Medical Service, Medical College of South Carolina, Charleston, South Carolina.

Paul H. Jordan, Jr., M.D.
Associate Professor of Surgery, University of Florida Medical Center, Gainesville, Florida.

John W. Kirklin, M.D., M.S. (Surg.)
Consultant, Section of Surgery, Mayo Clinic; Associate Professor of Surgery, Mayo Foundation, Graduate School, University of Minnesota, Rochester, Minnesota.

Chi Kong Liu, M.D.
Director, Cardio-Pulmonary Laboratory and Division of Cardiology, Department of Medicine, Los Angeles County Harbor General Hospital, Torrance, California; Assistant Clinical Professor and Lecturer in the Department of Medicine, University of California, Los Angeles, California.

Esther L. McCandless, Ph.D.
Formerly, Assistant Professor, Department of Physiology, University of Tennessee, Memphis, Tennessee. Presently, Research Physiologist, Chronic Disease Research Institute, University of Buffalo, Buffalo, New York.

John F. McGinty, M.D.
Formerly, Research Fellow, Wayne State University, College of Medicine, Detroit, Michigan.

Vince Moseley, M.D.
Professor of Medicine, Medical College of South Carolina, Charleston, South Carolina.

Arthur J. Moss, M.D.
Research Associate in Cardiology, U. S. Naval School of Aviation Medicine, Pensacola, Florida. Present address: Massachusetts General Hospital, Boston, Massachusetts.

V. A. Negovsky, M.D.
Chief of the Laboratory of Experimental Physiology for Resuscitation, Academy of Medical Sciences, Moscow, U.S.S.R.

Henry N. Neufeld, M.D.
Special Appointee, Mayo Foundation, Graduate School, University of Minnesota, Rochester, Minnesota; Cardiologist, Tel-Hashomer Government Hospital, Israel; on leave of absence.

Abraham Noordergraaf, Ph.D.
Visiting Fellow in Therapeutic Research, University of Pennsylvania, Philadelphia, Pennsylvania; Senior Research Officer, Department of Medical Physics, Physics Laboratory, University of Utrecht, Utrecht, The Netherlands.

Ronald T. Piccirillo, M.D.
Fellow in Cardiology, Los Angeles County Harbor General Hospital, Torrance, California.

H. Rawling Pratt-Thomas, M.D.
Professor of Pathology, Medical College of South Carolina, Charleston, South Carolina.

Timothy J. Regan, M.D.
Assistant Professor of Medicine, Seton Hall College of Medicine, Jersey City, New Jersey.

Richard S. Ross, M.D.
Associate Professor of Medicine, The Johns Hopkins University School of Medicine, Baltimore, Maryland.

Herbert E. Sloan, Jr., M.D.
Associate Professor, Department of Surgery, University of Michigan Medical School, Ann Arbor, Michigan.

Frank C. Spencer, M.D.
Associate Professor of Surgery, The Johns Hopkins University School of Medicine, Baltimore, Maryland.

Aaron M. Stern, M.D.
Associate Professor, Department of Pediatrics and Communicable Diseases, University of Michigan Medical School, Ann Arbor, Michigan.

Norman S. Talner, M.D.
Formerly, Assistant Professor, Department of Pediatrics and Communicable Diseases, University of Michigan Medical School, Ann Arbor, Michigan; Presently, Director of Pediatric Cardiopulmonary Laboratory; Assistant Professor, Department of Pediatrics, Yale University School of Medicine, New Haven, Connecticut.

Earl H. Wood, M.D., Ph.D.
Consultant, Section of Physiology, Mayo Clinic; Professor of Physiology, Mayo Foundation, Graduate School, University of Minnesota; Rochester, Minnesota.

Irving S. Wright, M.D.
Professor of Clinical Medicine, Cornell University College of Medicine; Attending Physician, The New York Hospital, New York City, New York.

D. B. Zilversmit, Ph.D.
Professor of Physiology, University of Tennessee Medical Units, Memphis, Tennessee. Established Investigator of the American Heart Association.

Eldred Zobl, M.D.
Instructor in Medicine, Veterans Administration Hospital, Dearborn, Michigan.